

BS

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 July 2004 (15.07.2004)

PCT

(10) International Publication Number
WO 2004/058718 A1

(51) International Patent Classification⁷: **C07D 217/24**,
A61K 31/472, 31/4725, C07D 401/12, 405/12, 417/12

(74) Agent: **DIXON, Lisa, A.**; Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, MA 02139 (US).

(21) International Application Number:
PCT/US2003/040870

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(22) International Filing Date:
22 December 2003 (22.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/435,133 20 December 2002 (20.12.2002) US

(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **VERTEX PHARMACEUTICALS INCORPORATED** [US/US]; 130 Waverly Street, Cambridge, MA 02139 (US).

(72) Inventors; and

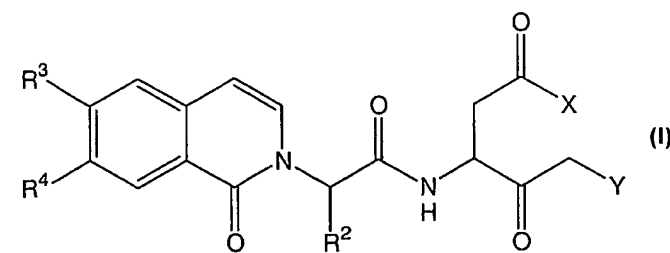
(75) Inventors/Applicants (*for US only*): **CHARRIER, Jean-Damien** [FR/GB]; 2 Easterfield Grove, Wantage, Oxfordshire OX12 7LL (GB). **MORTIMORE, Michael** [GB/GB]; Walrus House, 156 The Hill, Burford, Oxfordshire, OX18 4QY (GB). **STUDLEY, John, R.** [GB/GB]; 29 Willow Brook, Abingdon, Oxfordshire OX14 1TD (GB).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 4-OXO-3-(1-OXO-1H-ISOQUINOLIN-2-YLACETYLAMINO)-PENTANOIC ACID ESTER AND AMIDE DERIVATIVES AND THEIR USE AS CASPASE INHIBITORS



(57) Abstract: The present invention provides a compound of formula (I); wherein: X is -OR¹ or -N(R⁵)₂, Y is halo, trifluorophenoxy, or tetrafluorophenoxy; R¹ is: C₁₋₆ straight chained or branched alkyl, alkenyl, or alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with optionally substituted aryl, CF₃, C₁, F, OMe, OEt, OCF₃, CN, or NMe₂; C₁₋₆ cycloalkyl, wherein 1-2 carbon atoms in the cycloalkyl is optionally replaced with -O- or -NR⁵; R² is C₁₋₆ straight chained or branched alkyl; R³ is

hydrogen, halo, OCF₃, CN, or CF₃; R⁴ is hydrogen, halo, OCF₃, CN, or CF₃; and each R⁵ is independently H, C₁₋₆ straight chained or branched alkyl, aryl, -O-C₁₋₆ straight chained or branched alkyl, or -O-aryl. The present invention also provides pharmaceutical compositions and methods using such compositions for treating a caspase-mediated disease, particularly in the central nervous system.

4-OXO-3-(1-OXO-1H-ISOQUINOLIN-2-YLACETYLAMINO)-PENTANOIC ACID
ESTER AND AMIDE DERIVATIVES AND THEIR USE AS CASPASE INHIBITORS

[0001] This application claims the benefit of United States Provisional Application No. 60/435,133, filed December 20, 2002, which is incorporated herein by reference.

Field of the Invention

[0002] This invention relates to compounds, and compositions thereof, that are prodrugs of caspase inhibitors.

[0003] This invention also relates to processes for preparing these caspase inhibitor prodrugs.

[0004] This invention further relates to pharmaceutical compositions comprising said prodrugs and to the use of the compounds and compositions thereof for the treatment of diseases and disorders related to inflammatory or degenerative conditions.

Background of the Invention

[0005] Apoptosis, or programmed cell death, is a principal mechanism by which organisms eliminate unwanted cells. The deregulation of apoptosis, either excessive apoptosis or the failure to undergo it, has been implicated in a number of diseases such as cancer, acute inflammatory and autoimmune disorders, ischemic diseases and certain neurodegenerative disorders [see generally Science, 281, pp. 1283-1312 (1998); Ellis et al., Ann. Rev. Cell. Biol., 7, p. 663 (1991)].

[0006] Caspases are a family of cysteine protease enzymes that are key mediators in the signaling pathways for apoptosis and cell disassembly [N.A. Thornberry, Chem. Biol., 5, pp. R97-R103 (1998)]. These signaling pathways vary depending on cell type and stimulus, but

-2-

all apoptosis pathways appear to converge at a common effector pathway leading to proteolysis of key proteins. Caspases are involved in both the effector phase of the signaling pathway and further upstream at its initiation.

5 The upstream caspases involved in initiation events become activated and in turn activate other caspases that are involved in the later phases of apoptosis.

[0007] The utility of caspase inhibitors to treat a variety of mammalian disease states associated with an increase in cellular apoptosis has been demonstrated using peptidic caspase inhibitors. For example, in rodent models, caspase inhibitors have been shown to reduce infarct size and inhibit cardiomyocyte apoptosis after myocardial infarction, to reduce lesion volume and neurological deficit resulting from stroke, to reduce post-traumatic apoptosis and neurological deficit in traumatic brain injury, to be effective in treating fulminant liver destruction, and to improve survival after endotoxic shock [H. Yaoita et al., Circulation, 97, pp. 276-281 (1998); M. Endres et al., J. Cerebral Blood Flow and Metabolism, 18, pp. 238-247, (1998); Y. Cheng et al., J. Clin. Invest., 101, pp. 1992-1999 (1998); A.G. Yakovlev et al., J. Neurosci., 17, pp. 7415-7424 (1997); I. Rodriguez et al., J. Exp. Med., 184, pp. 2067-2072 (1996); Grobmyer et al., Mol. Med., 5, p. 585 (1999)]. However, due to their peptidic nature, such inhibitors are typically characterized by undesirable pharmacological properties, such as poor cellular penetration and cellular activity, poor oral absorption, poor stability and rapid metabolism [J.J. Plattner and D.W. Norbeck, in Drug Discovery Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126]. This has hampered their development

-3-

into effective drugs. These and other studies with peptidic caspase inhibitors have demonstrated that an aspartic acid residue is involved in a key interaction with the caspase enzyme [K.P. Wilson et al., Nature, 370, 5 pp. 270-275 (1994); Lazebnik et al., Nature, 371, p. 346 (1994)].

[0008] Accordingly, peptidyl and non-peptidyl aspartic acid compounds are useful as caspase inhibitors. For examples, WO96/03982 reports azaaspartic acid analogs 10 effective as interleukin-1 β converting enzyme ("ICE") inhibitors.

[0009] However, due to their acidic nature such peptidic and non-peptidyl aspartic acid derivatives are charged at physiological pH. This has inhibited their 15 ability to cross the blood brain barrier and to penetrate cells at therapeutically useful levels.

[0010] Accordingly, it would be advantageous to have drug derivatives that are targeted at the diseased organs, especially the brain and central nervous system. 20 In addition, it would be advantageous to have drug derivatives that are targeted at the diseased cells rather than at healthy cells, thus reducing undesirable side-effects.

[0011] The use of prodrugs to impart desired 25 characteristics such as increased bioavailability or increased site-specificity for known drugs is a recognized concept. The use of pro-drugs to deliver compounds across the Blood-Brain barrier (BBB) is also well known. Bradley D. Anderson, "Prodrugs for Improved 30 CNS Delivery" in Advanced Drug Delivery Reviews (1996), 19, 171-202 provides a review of the area. In particular, the use of alkyl esters of chloambucil have

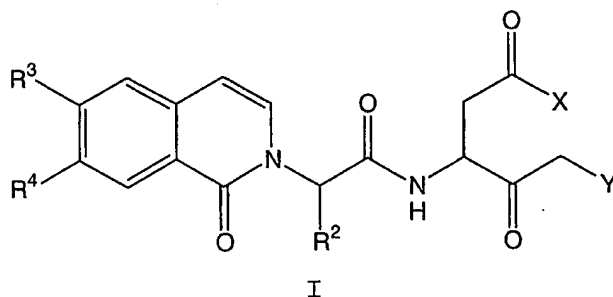
-4-

been used to enhance brain penetration (Cancer Chemother. Pharmacol. (1990), 25, 311-319); the use of benzoyl esters of dopamine have been used to enhance delivery across BBB (Naunyn-Schmiedeberg's Arch. Pharmacol., (1988), 338(5), 497-503); lipophilic esters of a leucine-enkephalin analogue have been used for brain-targeted delivery (J. Med. Chem., (1996), 39(24), 4775-4782). Disulphide-based esters of L-DOPA have been shown to increase brain levels of DOPA in the rat brain up to 30 fold (Int. J. Pharmaceutics, (1995), 116, 51-63). The tyrosine ester of nipecotic acid showed *in vivo* effects consistent with BBB penetration (J. Pharma. Sci., (1999), 88(5), 561) and D-glucose esters of 7-chlorokynurenic acid are available to CNS and are anti-convulsive *in vivo* (Brain Res., (2000), 860, 149-156).

[0012] A need nevertheless exists for prodrugs of caspase inhibitors that have the ability to cross the blood brain barrier and penetrate the brain and central nervous system at therapeutically useful levels.

Summary of the Invention

[0013] The present invention provides a compound of formula I:



wherein:

X is -OR¹ or -N(R⁵)₂,

Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R¹ is:

-5-

C₁₋₆ straight chained or branched alkyl, alkenyl, or alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with aryl, CF₃, Cl, F, OMe, OEt, OCF₃, CN, or NMe₂;

5 C₁₋₆ cycloalkyl, wherein 1-2 carbon atoms in the cycloalkyl is optionally replaced with -O- or -NR⁵-;

R² is C₁₋₆ straight chained or branched alkyl;

R³ is hydrogen, halo, OCF₃, CN, or CF₃;

R⁴ is hydrogen, halo, OCF₃, CN, or CF₃; and

10 each R⁵ is independently H, C₁₋₆ straight chained or branched alkyl, aryl, -O-C₁₋₆ straight chained or branched alkyl, or -O-aryl.

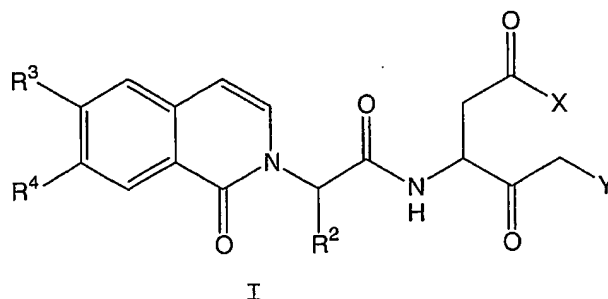
[0014] The present invention also provides processes for preparing these compounds, compositions,
15 pharmaceutical compositions, and methods using such compounds and compositions for inhibiting caspases and methods for treating caspase-mediated diseases, particularly a caspase-mediated diseases in the central nervous system.

20 Detailed Description of the Invention

[0015] The present invention provides pro-drug esters, amides, or hydroxamides of caspase inhibitors that have an improved ability, relative to the corresponding drug, of crossing the blood-brain barrier. Inside the blood-
25 brain barrier, the pro-drugs have the ability to undergo cleavage and provide a caspase inhibitor within the brain.

[0016] According to one embodiment (A), this invention provides a compound of formula I:

-6-



wherein:

X is $-OR^1$ or $-N(R^5)_2$,

5 Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R^1 is:

C_{1-6} straight chained or branched alkyl,
 alkenyl, or alkynyl, wherein the alkyl, alkenyl, or
 alkynyl is optionally substituted with aryl, CF_3 , Cl, F,
 10 OMe, OEt, OCF_3 , CN, or NMe_2 ;

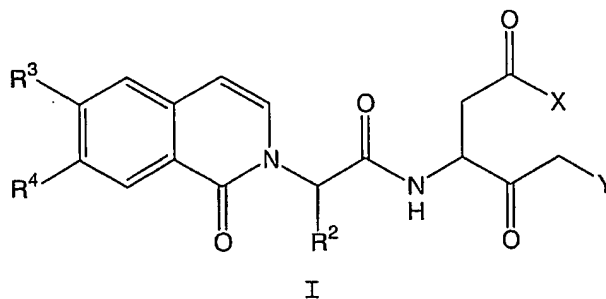
C_{1-6} cycloalkyl, wherein 1-2 carbon atoms in the
 cycloalkyl is optionally replaced with $-O-$ or $-NR^5-$;

R^2 is C_{1-6} straight chained or branched alkyl;

R^3 is hydrogen, halo, OCF_3 , CN, or CF_3 ;

15 R^4 is hydrogen, halo, OCF_3 , CN, or CF_3 ; and
 each R^5 is independently H, C_{1-6} straight chained or
 branched alkyl, aryl, $-O-C_{1-6}$ straight chained or branched
 alkyl, or $-O$ -aryl.

[0017] According to another embodiment (B), this
 20 invention provides compound of formula I:



wherein:

X is $-OR^1$ or $-N(R^5)_2$,

-7-

Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R¹ is:

C₁₋₆ straight chained or branched alkyl,
alkenyl, or alkynyl, wherein the alkyl, alkenyl, or
5 alkynyl is optionally substituted with aryl, CF₃, Cl, F,
OMe, OEt, OCF₃, CN, or NMe₂;

C₁₋₆ cycloalkyl, wherein 1-2 carbon atoms in the
cycloalkyl is optionally replaced with -O- or -NR⁵-;

R² is C₁₋₆ straight chained or branched alkyl;

10 R³ is hydrogen, halo, OCF₃, CN, or CF₃;

R⁴ is hydrogen, halo, OCF₃, CN, or CF₃; and

R⁵ is H, C₁₋₆ straight chained or branched alkyl, or
-O-C₁₋₆ straight chained or branched alkyl; provided that
if:

15 Y is F;

R² is isopropyl, R³ is hydrogen, and R⁴ is Cl; or

R² is ethyl, R³ is hydrogen, and R⁴ is Cl or CF₃; or

R² is ethyl, R³ is Cl or CF₃, and R⁴ is hydrogen; then

R¹ is not t-butyl; and if

20 Y is 2,3,5,6-tetrafluorophenoxy;

R² is ethyl; and

R³ and R⁴ are each hydrogen; or

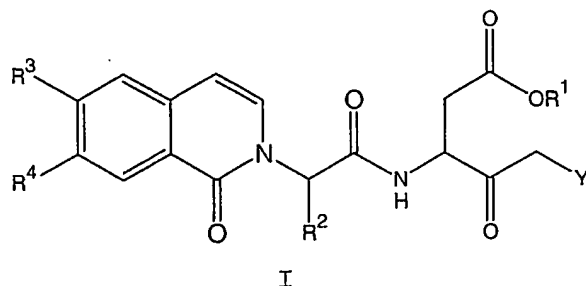
R³ is hydrogen and R⁴ is Cl or CF₃; or

R³ and R⁴ are each Cl; then

25 R¹ is not t-butyl.

-8-

[0018] The present invention also provides in another embodiment (C) a compound of formula I:



5 wherein:

Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R¹ is C₁₋₆ straight chained or branched alkyl optionally substituted with phenyl or CF₃;

R² is C₁₋₆ straight chained or branched alkyl;

10 R³ is hydrogen, halo, OCF₃, CN, or CF₃; and

R⁴ is hydrogen, halo, OCF₃, CN, or CF₃.

An alternative form of embodiment C provides that if:

Y is F;

15 R² is ethyl; and

R³ is hydrogen and R⁴ is Cl or CF₃; or

R³ is Cl or CF₃ and R⁴ is hydrogen; then

R¹ is not t-butyl; and if

Y is 2,3,5,6-tetrafluorophenoxy;

20 R² is ethyl; and

R³ and R⁴ are each hydrogen; or

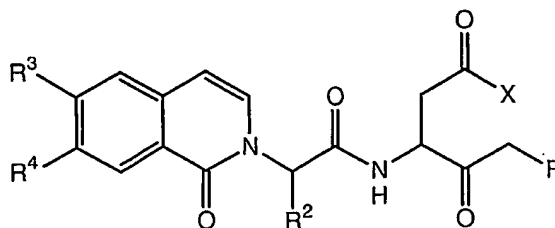
R³ is hydrogen and R⁴ is Cl; or

R³ and R⁴ are each Cl; then

R¹ is not t-butyl.

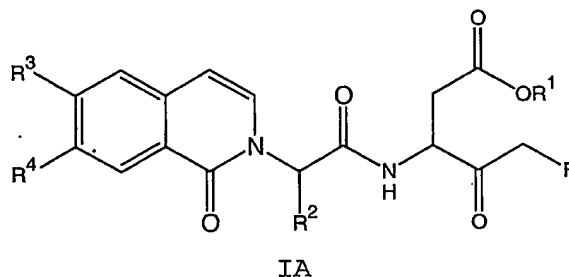
25 [0019] According to another embodiment, the present invention provides a compound of formula IA':

-9-



wherein X, R², R³, and R⁴ are as defined in any of the embodiments herein.

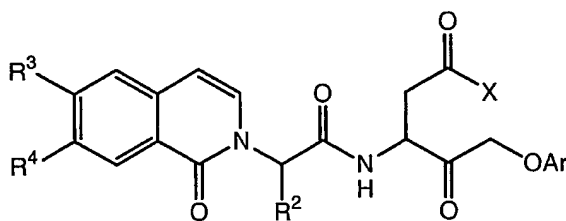
[0020] According to another embodiment, the present invention provides a compound of formula IA:



wherein:

- 5 R¹, R², R³, and R⁴ are as defined in any of the embodiments herein.

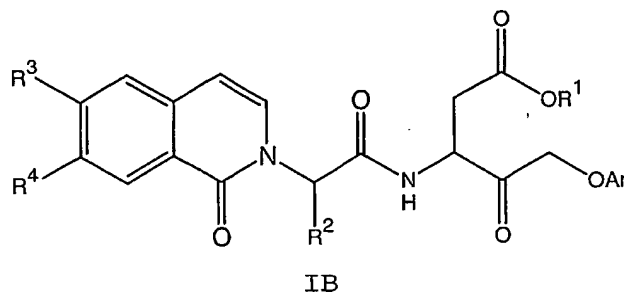
[0021] According to another embodiment, the present invention provides a compound of formula IB':



- 10 wherein X, R², R³, R⁴, and Ar are as defined in any of the embodiments herein.

[0022] According to another embodiment, the present invention provides a compound of formula IB:

-10-



wherein:

Ar, R¹, R², R³, and R⁴ are as defined in any of the
 5 embodiments herein.

[0023] More specific embodiments of formulae I, IA, IA', IB, and IB' are as defined below.

[0024] R¹ is an alkyl group that is not substituted with phenyl or CF₃. Preferably, R¹ is a t-butyl group.
 10 Alternatively, R¹ is not a t-butyl group. More preferably, R¹ is ethyl or propyl.

[0025] R² is ethyl, n-propyl, or isopropyl. More preferably, R² is ethyl.

[0026] Y is F, trifluorophenoxy, or tetrafluorophenoxy.

[0027] Ar is 2,3,5,6-tetrafluorophenyl.

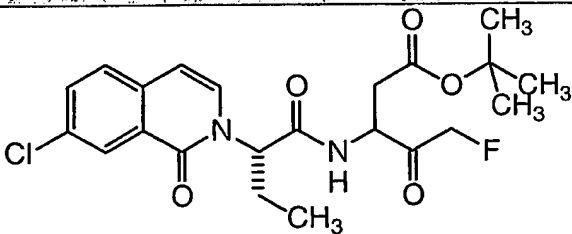
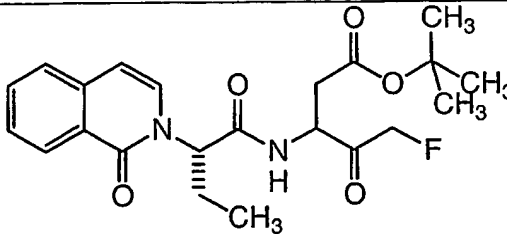
[0028] R³ is hydrogen and R⁴ is halo, OCF₃, CN, or CF₃.
 15 Alternatively, R³ is hydrogen and R⁴ is F, Cl, or CF₃. In another embodiment, R³ is hydrogen and R⁴ is halo. Alternatively, R³ is hydrogen and R⁴ is chloro.

[0029] In one embodiment, X is -OR¹. One form of this embodiment provides a compound wherein the R¹ of X is an
 20 alkyl group that is not substituted with phenyl or CF₃. Two other forms of this embodiment are those wherein the alkyl group is substituted with phenyl or CF₃. Another form provides a compound wherein the R¹ of X is not t-butyl. Yet another form of this embodiment provides a
 25 compound wherein the R¹ of X is ethyl or propyl.

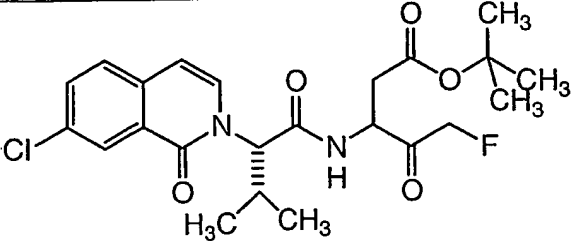
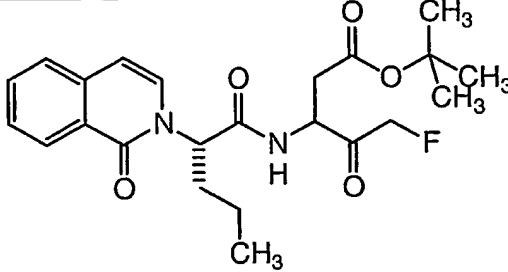
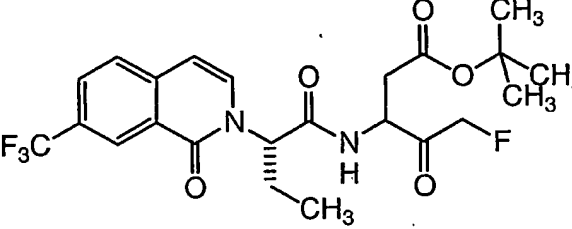
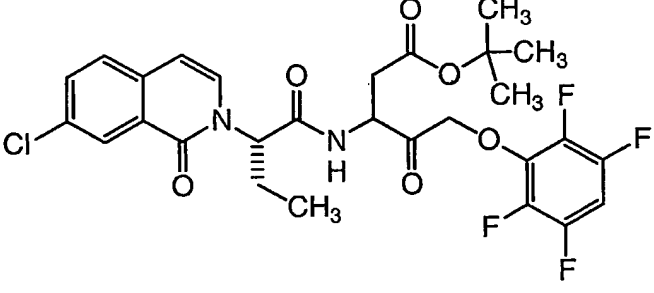
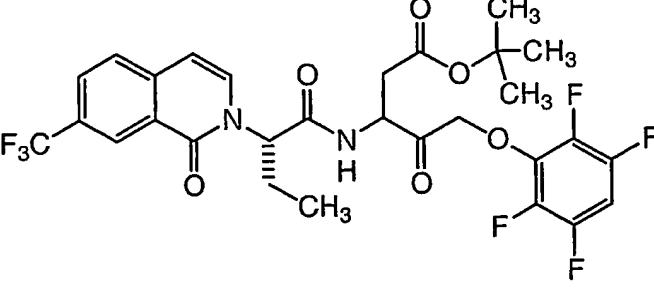
-11-

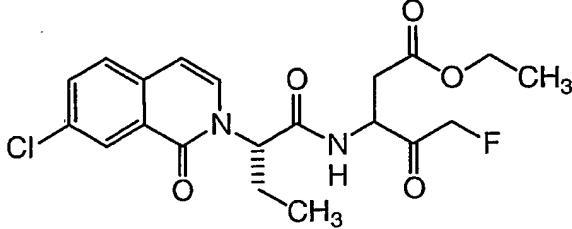
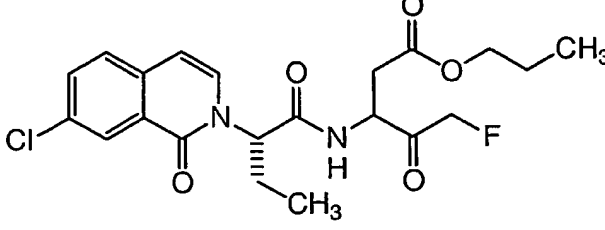
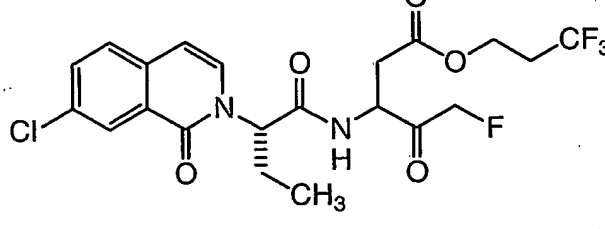
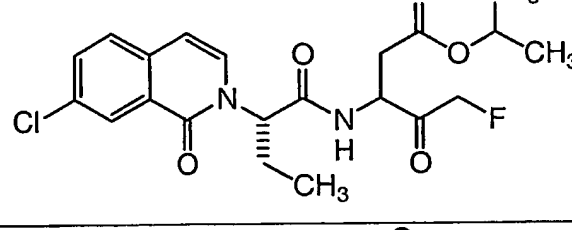
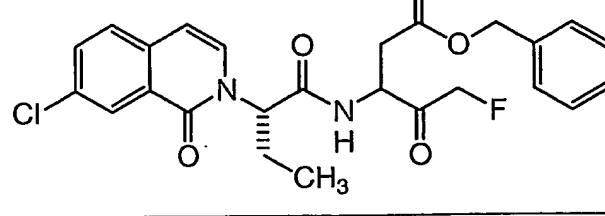
- [0030] In another embodiment, X is $-N(R^5)_2$. One form of this embodiment provides a compound wherein one R^5 is C_{1-6} straight chained or branched alkyl and the other R^5 is $-O-C_{1-6}$ straight chained or branched alkyl. Another form provides a compound wherein one R^5 is H or $-C_{1-6}$ straight chained or branched alkyl and the other R^5 is $-C_{1-6}$ straight chained or branched alkyl. In any of the embodiments herein, R^5 is preferably methyl, ethyl, or propyl.
- 10 [0031] In one embodiment, if X comprises an aryl, the aryl is optionally substituted phenyl.
- [0032] In another embodiment, if Y is halo, then both R^3 and R^4 are not simultaneously hydrogen.
- [0033] The embodiments herein may be combined to provide a compound according to this invention.
- 15 [0034] According to a more preferred embodiment, the present invention provides a compound selected from Table 1 below:

Table 1

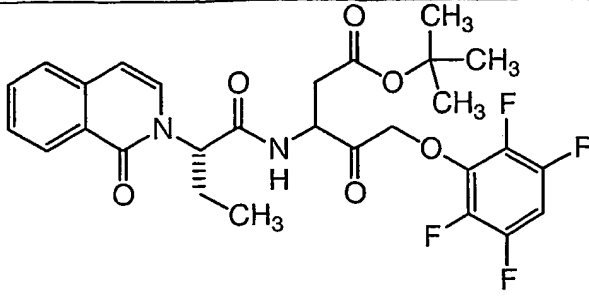
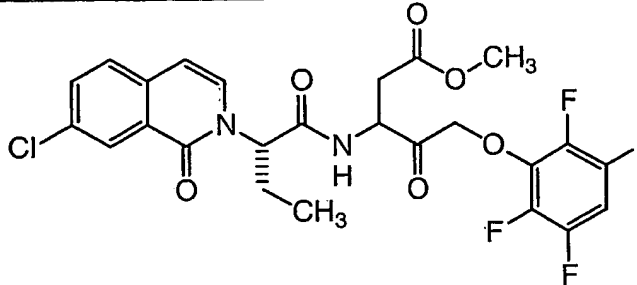
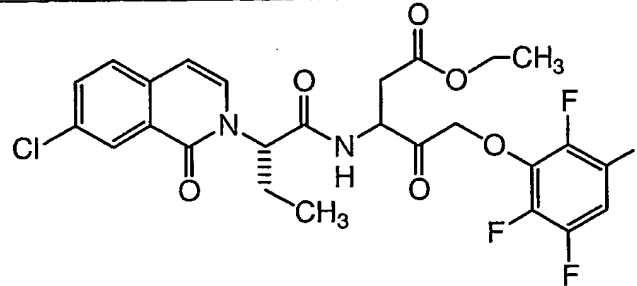
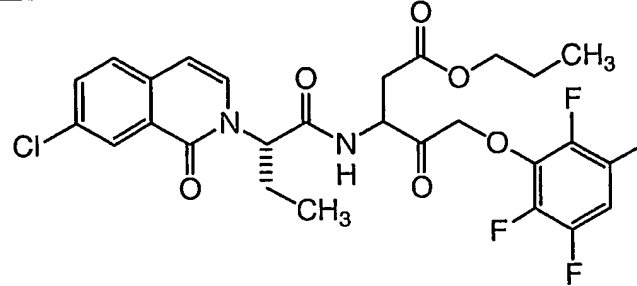
Example	Structure
1	
2	

-12-

Example	Structure
3	
4	
5	
6	
7	

Example	Structure
8	
9	
10	
11	
12	

-14-

Example	Structure
13	
14	
15	
16	

[illegible]

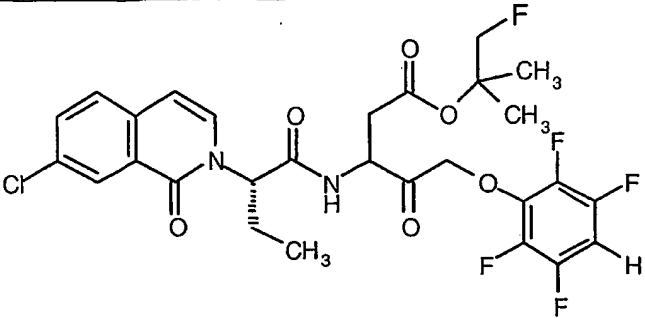
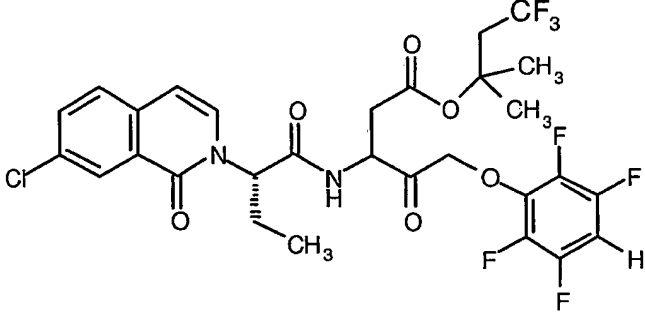
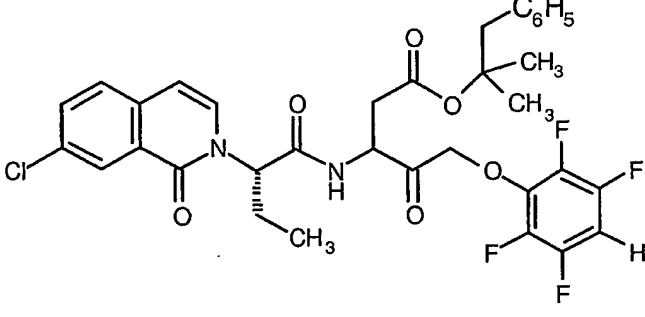
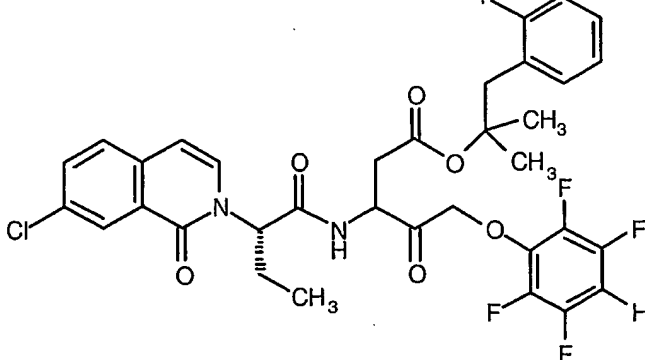
Example	Structure
22	
23	
24	
25	

-17-

Example	Structure
26	 <chem>CC(C)C(=O)OCC(=O)N[C@@H](C)C(=O)N1C(=O)c2ccc(Cl)cc2N1C(=O)C3=CC(=CC(=C3)F)F</chem>
27	 <chem>CCC(C)C(=O)OCC(=O)N[C@@H](C)C(=O)N1C(=O)c2ccc(Cl)cc2N1C(=O)C3=CC(=CC(=C3)F)F</chem>
28	 <chem>C1CCCCC1C(=O)OCC(=O)N[C@@H](C)C(=O)N1C(=O)c2ccc(Cl)cc2N1C(=O)C3=CC(=CC(=C3)F)F</chem>
29	 <chem>CC(C)C(=O)OCC(=O)N[C@@H](C)C(=O)N1C(=O)c2ccc(Cl)cc2N1C(=O)C3=CC(=CC(=C3)F)F</chem>

Example	Structure
30	
31	
32	
33	

[illegible]

Example	Structure
38	
39	
40	
41	

Example	Structure
42	
43	
44	

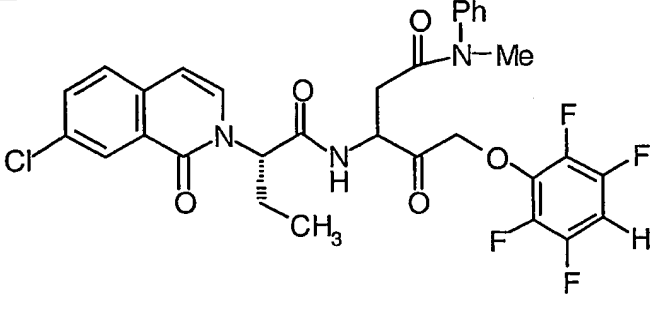
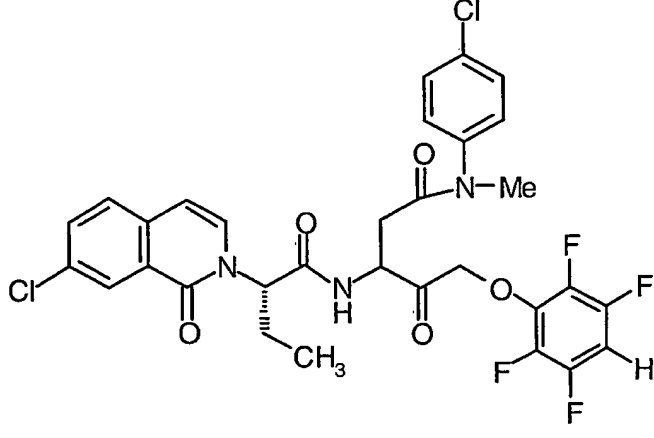
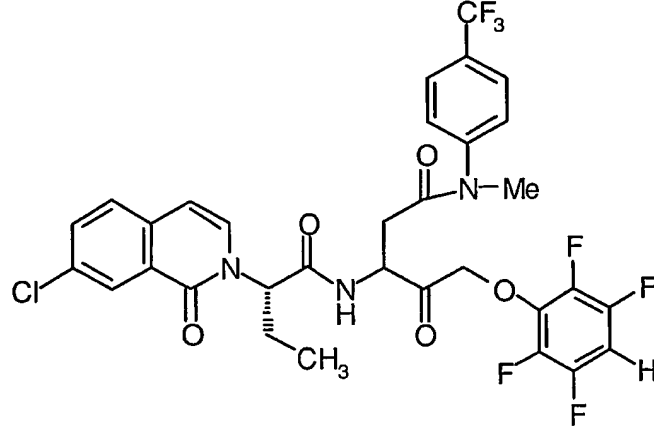
[illegible]

Example	Structure
48	
49	
50	

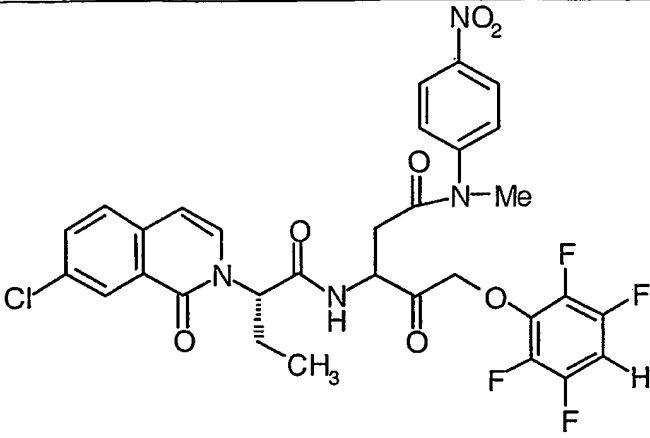
Example	Structure
51	
52	
53	
54	

Example	Structure
55	
56	
57	
58	

-26-

Example	Structure
59	 <p>Chemical structure of Example 59: A 6-chloroquinolin-2(1H)-one derivative. The nitrogen at position 1 is substituted with a 1-ethyl-3-oxo-1-(2-oxo-2-(2-(2,4,6-trifluorophenoxy)ethyl)-3-oxopropyl)ammonioethyl group. The ethyl group is shown with a dashed bond to the chiral center.</p>
60	 <p>Chemical structure of Example 60: A 6-chloroquinolin-2(1H)-one derivative. The nitrogen at position 1 is substituted with a 1-ethyl-3-oxo-1-(2-oxo-2-(2-(2,4,6-trifluorophenoxy)ethyl)-3-oxopropyl)ammonioethyl group. The ethyl group is shown with a dashed bond to the chiral center. The 2-oxo-2-(2-(2,4,6-trifluorophenoxy)ethyl)-3-oxopropyl group is substituted with a 4-chlorophenyl group via a carbonyl linkage.</p>
61	 <p>Chemical structure of Example 61: A 6-chloroquinolin-2(1H)-one derivative. The nitrogen at position 1 is substituted with a 1-ethyl-3-oxo-1-(2-oxo-2-(2-(2,4,6-trifluorophenoxy)ethyl)-3-oxopropyl)ammonioethyl group. The ethyl group is shown with a dashed bond to the chiral center. The 2-oxo-2-(2-(2,4,6-trifluorophenoxy)ethyl)-3-oxopropyl group is substituted with a 4-(trifluoromethyl)phenyl group via a carbonyl linkage.</p>

-27-

Example	Structure
62	

[0035] In certain embodiments of this invention, the variables are as defined in the compounds of Table 1.

[0036] As used herein, an "aromatic group" or "aryl" refers to a 5-10-membered ring that contains at least one aromatic ring and up to 3 heteroatoms independently selected from N, N(R⁷), O, S, SO, or SO₂. Preferred aromatic rings include phenyl, pyridyl, and thiazole.

[0037] An aryl group herein is optionally substituted with one or more (preferably 1, 2, or 3) groups selected independently from halogen, -OR⁷, -OC(O)N(R⁷)₂, -NO₂, -CN, -CF₃, -OCF₃, -R⁷, oxo, thioxo, 1,2-methylenedioxy, 1,2-ethylenedioxy, -N(R⁷)₂, -SR⁷, -SOR⁷, -SO₂R⁷, -SO₂N(R⁷)₂, -SO₃R⁷, -C(O)R⁷, -C(O)C(O)R⁷, -C(O)CH₂C(O)R⁷, -C(S)R⁷, -C(O)OR⁷, -OC(O)R⁷, -C(O)N(R⁷)₂, -OC(O)N(R⁷)₂, -C(S)N(R⁷)₂, -(CH₂)₀₋₂NHC(O)R⁷, -N(R⁷)N(R⁷)COR⁷, -N(R⁷)N(R⁷)C(O)OR⁷, -N(R⁷)N(R⁷)CON(R⁷)₂, -N(R⁷)SO₂R⁷, -N(R⁷)SO₂N(R⁷)₂, -N(R⁷)C(O)OR⁷, -N(R⁷)C(O)R⁷, -N(R⁷)C(S)R⁷, -N(R⁷)C(O)N(R⁷)₂, -N(R⁷)C(S)N(R⁷)₂, -N(COR⁷)COR⁷, -N(OR⁷)R⁷, -C(=NH)N(R⁷)₂, -C(O)N(OR⁷)R⁷, -C(=NOR⁷)R⁷, -OP(O)(OR⁷)₂, -P(O)(R⁷)₂, -P(O)(OR⁷)₂, and -P(O)(H)(OR⁷); wherein R⁷ is hydrogen-,

-28-

(C1-C12)-aliphatic-, (C3-C10)-cycloaliphatic -, (C3-C10)-cycloaliphatic]-(C1-C12)-aliphatic-, (C6-C10)-aryl-, (C6-C10)-aryl-(C1-C12)aliphatic-, (C3-C10)-heterocyclyl-, (C6-C10)-heterocyclyl-(C1-C12)aliphatic-, (C5-C10)-heteroaryl-, or (C5-C10)-heteroaryl-(C1-C12)-aliphatic-.

[0038] Preferred substituents are independently selected from halogen (particularly F or Cl), alkyl (particularly CH₃), fluoroalkyl (particularly CF₃), CN, alkoxy (particularly OMe), fluoroalkoxy (particularly OCF₃), -NO₂, and N(R⁵)₂ (particularly NMe₂).

[0039] According to another embodiment, the present invention provides a pharmaceutical composition comprising:

a) a compound of the invention, as defined herein, or a pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable carrier, adjuvant or vehicle.

[0040] According to a preferred embodiment, the pharmaceutical composition of the present invention comprises:

a) a compound of formula I, IA, IA' IB, or IB'; and

b) a pharmaceutically acceptable carrier, adjuvant or vehicle.

[0041] According to a more preferred embodiment, the pharmaceutical composition of the present invention comprises a compound selected from Table 1 above.

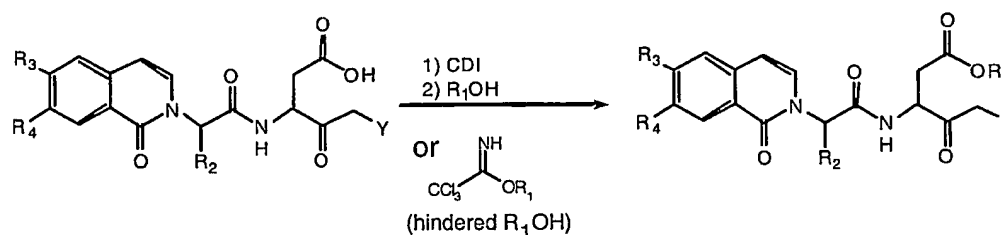
[0042] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms or hydrated forms, all such forms of the compounds being within the scope of the invention. Unless otherwise stated, structures depicted herein are

-29-

also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0043] The compounds of this invention may be obtained by any method, including general, synthetic methods known to those skilled in the art for analogous compounds (see e.g., WO 01/42216). For the purposes of illustration, the following Schemes for the synthesis of the compounds of the present invention are provided. The Schemes that depict the preparation of compound wherein X is $-\text{OR}^1$ may be modified by routine methods to produce compounds wherein X is or $-\text{N}(\text{R}^5)_2$.

Scheme I



I'

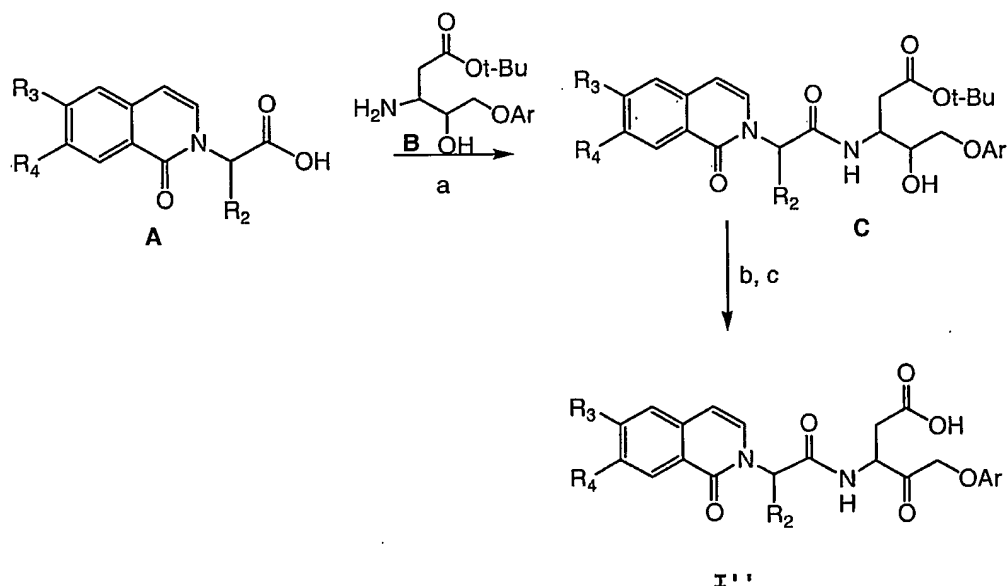
I

[0044] In Scheme I above, the following abbreviations are used: CDI is 1,1'-carbonyldiimidazole. Scheme I

-30-

depicts formation of prodrug esters of formula I. Acid I' is reacted under standard esterification conditions. In Scheme I the conditions depicted include reacting acid I' in the presence of CDI and then in the presence of an appropriate alcohol.

Scheme II

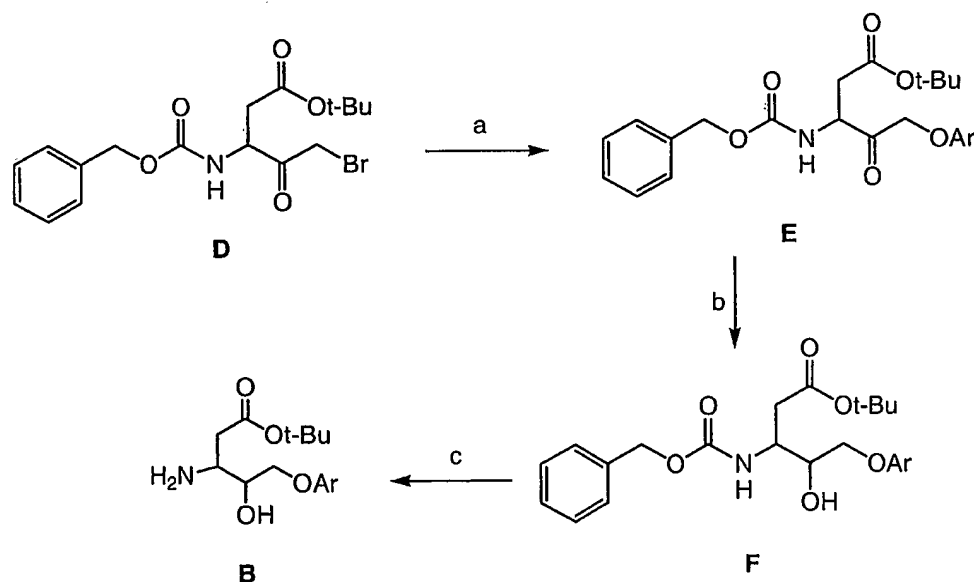


Scheme II (a) EDC/DMAP/HOBT/THF; (b) Dess-Martin periodinane; (c) TFA/DCM.

[0045] In Scheme II above, the following abbreviations are used: EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; HOBT is 1-hydroxybenzotriazole; THF is tetrahydrofuran; TFA is trifluoroacetic acid; DCM is dichloromethane; DMAP is 4-dimethylaminopyridine. Acid A is coupled to amino alcohol B to provide C. In Scheme II, the coupling conditions depicted involve reacting Acid A and amino alcohol B in the presence of EDC, DMAP, and HOBT in THF. Other acid-amino coupling conditions could be used and would be known to skilled practitioners. In the case of fluoromethyl ketones where

-31-

CH₂OAr is replaced by CH₂F, the amino alcohol B may be obtained according to the method of Revesz et al., *Tetrahedron Lett.* 1994, 35, 9693 (which is incorporated herein by reference). In the case of fluoro-substituted phenoxy ketones where Ar is 2,3,5,6-tetrafluorophenoxy, 2,4,6-trifluorophenoxy, or 2,3,6-trifluorophenoxy, the amino alcohol B may be obtained by methods analogous to those of Semple et al., *Bioorganic and Medicinal Chemistry Letters*, 1997, 7, 1337 (Scheme III). C is converted to I'' by oxidization under appropriate conditions (e.g., by using Dess-Martin periodinane as depicted here) followed by deprotection under hydrolysis conditions.

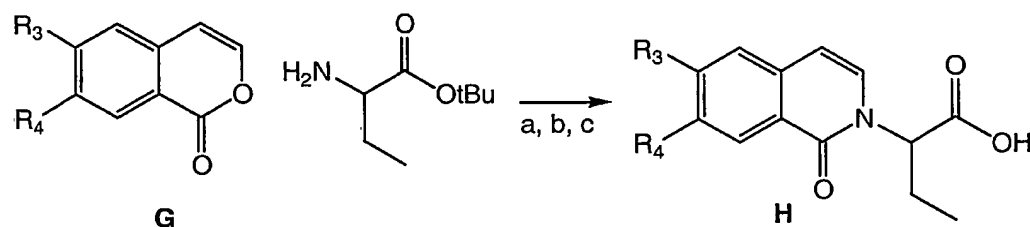
15 Scheme III

Scheme III (a) KF/DMF/ArOH; (b) NaBH₄/THF; (c) H₂/Pd/C/MeOH

[0046] In scheme III above, the following abbreviations are used: KF is potassium fluoride; DMF is N,N-dimethylformamide; ArOH is either 2,3,5,6-tetrafluorophenol, 2,4,6-trifluorophenol or 2,3,6-trifluorophenol; THF is tetrahydrofuran; MeOH is methanol.

-32-

Commercially available bromoketone D is reacted with the appropriately substituted fluorophenol and potassium fluoride to give phenoxy ketone E. The ketone is then reduced with sodium borohydride to give the alcohol F, which is hydrogenated using palladium on carbon as catalyst to give the amino alcohol B (in formula I, Y=fluoro-substituted phenoxy).

Scheme IV

10

Scheme IV (a) heat; (b) CHCl₃/IPA; (c) TFA/DCM

[0047] In Scheme IV the following abbreviations are used: IPA is isopropyl alcohol; TFA is trifluoroacetic acid and DCM is dichloromethane. Isoquinolin-1-one acid derivatives can be prepared in chiral form using the synthetic sequence shown in Scheme IV. The starting isocoumarin G is prepared by methods analogous to Narasimhan et al. Synthesis 1975, 797 and Margaretha et al. Tetrahedron 2000, 56, 6763 unless stated otherwise. Isocoumarin G is first heated with commercially available (S)-2-aminobutyric acid, tert-butyl ester. The resulting compound is reacted with concentrated hydrochloric acid in isopropanol to give the isoquinolin-1-one tert-butyl ester that is deprotected to provide the acid H using trifluoroacetic acid. The acid is then coupled to amino alcohol B (Scheme II).

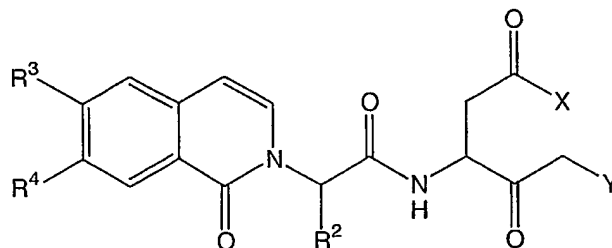
20

25

[0048] Accordingly, this invention also provides a process for preparing a compound of this invention.

-33-

[0049] One embodiment provides a process for preparing a compound of formula I:



5

I

wherein:

X is $-OR^1$ or $-N(R^5)_2$,

Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R^1 is:

10

C_{1-6} straight chained or branched alkyl, alkenyl, or alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with aryl, CF_3 , Cl, F, OMe, OEt, OCF_3 , CN, or NMe_2 ;

C_{1-6} cycloalkyl, wherein 1-2 carbon atoms in the cycloalkyl is optionally replaced with $-O-$ or $-NR^5-$;

15

R^2 is C_{1-6} straight chained or branched alkyl;

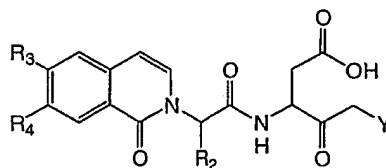
R^3 is hydrogen, halo, OCF_3 , CN, or CF_3 ;

R^4 is hydrogen, halo, OCF_3 , CN, or CF_3 ; and

R^5 is H, C_{1-6} straight chained or branched alkyl, aryl, $-O-C_{1-6}$ straight chained or branched alkyl, or $-O-$ aryl;

20

comprising the step of reacting a compound of formula I':



25

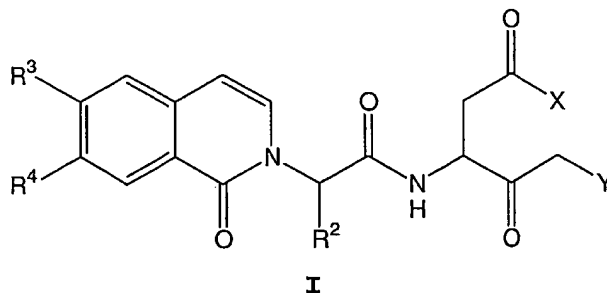
I'

wherein X, Y, R^2 , R^3 , and R^4 are as defined for formula I;

-34-

under conditions forming an ester or amide bond to provide a compound of formula I.

[0050] Another embodiment provides a process for preparing a compound of formula I:



wherein:

X is $-OR^1$ or $-N(R^5)_2$,

Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R^1 is:

C_{1-6} straight chained or branched alkyl, alkenyl, or alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with aryl, CF_3 , Cl, F, OMe, OEt, OCF_3 , CN, or NMe_2 ;

C_{1-6} cycloalkyl, wherein 1-2 carbon atoms in the cycloalkyl is optionally replaced with $-O-$ or $-NR^5-$;

R^2 is C_{1-6} straight chained or branched alkyl;

R^3 is hydrogen, halo, OCF_3 , CN, or CF_3 ;

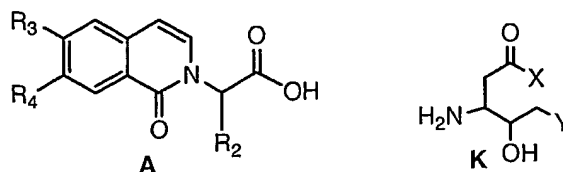
R^4 is hydrogen, halo, OCF_3 , CN, or CF_3 ; and

R^5 is H, C_{1-6} straight chained or branched alkyl, aryl, $-O-C_{1-6}$ straight chained or branched alkyl, or $-O-$ aryl;

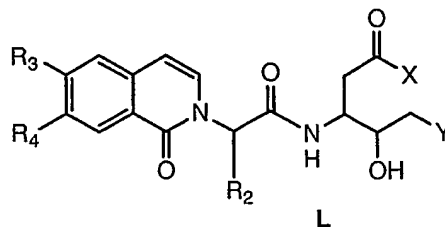
comprising the step of coupling a compound of formula A and a compound of formula K:

25

-35-

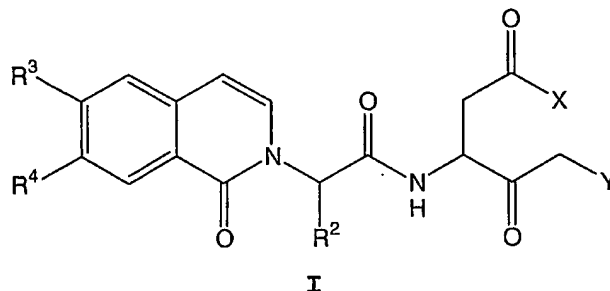


to provide a compound of formula L:



5 wherein X, Y, R^1 , R^2 , R^3 , and R^4 are as defined in formula I and wherein the hydroxy group in K is optionally protected.

[0051] Another embodiment provides a process for preparing a compound of formula I:



wherein:

X is $-OR^1$ or $-N(R^5)_2$,

Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

15 R^1 is:

C_{1-6} straight chained or branched alkyl, alkenyl, or alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with aryl, CF_3 , Cl, F, OMe, OEt, OCF_3 , CN, or NMe_2 ;

20 C_{1-6} cycloalkyl, wherein 1-2 carbon atoms in the cycloalkyl is optionally replaced with $-O-$ or $-NR^5-$;

R^2 is C_{1-6} straight chained or branched alkyl;

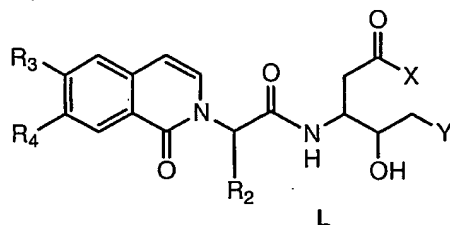
-36-

R^3 is hydrogen, halo, OCF_3 , CN, or CF_3 ;

R^4 is hydrogen, halo, OCF_3 , CN, or CF_3 ; and

R^5 is H, C_{1-6} straight chained or branched alkyl, aryl, $-O-C_{1-6}$ straight chained or branched alkyl, or $-O-$ aryl;

comprising the step of oxidizing a compound of formula L:



wherein X, Y, R^1 , R^2 , R^3 , and R^4 are as defined for formula I; to provide a compound of formula I.

[0052] In preferred embodiments, the above processes are as described herein (e.g., in the schemes, examples, and accompanying description).

[0053] The compounds of this invention may be assayed for their ability to inhibit apoptosis, the release of IL- 1β or caspase activity directly. Assays for each of the activities are known in the art. However, as would be recognized by a skilled practitioner, the prodrug compounds of this invention should be active only in assays where the prodrug moiety would be cleaved, typically in *in vivo* assays.

[0054] If pharmaceutically acceptable salts of the compounds of this invention are utilized in these compositions, those salts are preferably derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor

-37-

sulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, 5 hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base 10 salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as 15 arginine, lysine, and so forth.

[0055] Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, 20 diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

25 **[0056]** The compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase 30 biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow

-38-

administration by injection, alter metabolism and alter rate of excretion.

[0057] Pharmaceutically acceptable carriers that may be used in these compositions include, but are not
5 limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or
10 electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium
15 carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0058] According to a preferred embodiment, the compositions of this invention are formulated for
20 pharmaceutical administration to a mammal, preferably a human being.

[0059] Such pharmaceutical compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally,
25 vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion
30 techniques. Preferably, the compositions are administered orally or intravenously.

[0060] Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension.

-39-

These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0061] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are

-40-

commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

5 [0062] Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

15 [0063] The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

25 [0064] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

30 [0065] For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention

-41-

include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0066] For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

[0067] The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0068] The above-described compositions are particularly useful in therapeutic applications relating to an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an

-42-

infectious disease, a degenerative disease, a disease associated with cell death, an excess dietary alcohol intake disease, a viral mediated disease, retinal disorders, uveitis, inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, atopic dermatitis, scarring, graft vs host disease, organ transplant rejection, organ apoptosis after burn injury, osteoporosis, leukemias and related disorders, myelodysplastic syndrome, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, hemorrhagic shock, sepsis, septic shock, burns, Shigellosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, Kennedy's disease, prion disease, cerebral ischemia, epilepsy, myocardial ischemia, acute and chronic heart disease, myocardial infarction, congestive heart failure, atherosclerosis, coronary artery bypass graft, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related encephalitis, aging, alopecia, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, spinal cord injury, hepatitis-B, hepatitis-C, hepatitis-G, yellow fever, dengue fever, Japanese encephalitis, various forms of liver disease, renal disease, polycystic kidney disease, H. pylori-associated gastric and duodenal ulcer disease, HIV infection,

-43-

tuberculosis, and meningitis. The compounds and compositions are also useful in treating complications associated with coronary artery bypass grafts. The compounds and compositions are also useful for decreasing IGIF or IFN- γ production. The compounds and compositions are also useful in immunotherapy as a cancer treatment.

[0069] The compounds and compositions of this invention are particularly useful in therapeutic applications relating to inhibition of caspase activity in the central nervous system and/or the brain. These applications include treating neurological damage due to stroke, traumatic brain injury, and spinal cord injury.

[0070] The compounds and compositions may also be used in methods for preserving cells. These methods would be useful for preserving organs, particularly those intended for transplant, or blood products.

[0071] According to another embodiment, the compositions of this invention may further comprise another therapeutic agent. Such agents include, but are not limited to, thrombolytic agents such as tissue plasminogen activator and streptokinase. When a second agent is used, the second agent may be administered either as a separate dosage form or as part of a single dosage form with the compounds or compositions of this invention.

10 [0072] The amount of compound present in the compositions of this invention should be sufficient to cause a detectable decrease in the severity of the disease or in caspase activity and/or cell apoptosis, as measured by any of the assays known in the art.

15 [0073] Dosage levels of between about 0.01 and about 50 or about 100 mg/kg body weight per day, preferably

-44-

between 0.5 and about 75 mg/kg body weight per day and most preferably between about 1 and about 25 or about 50 mg/kg body weight per day of the active ingredient compound are useful in a monotherapy.

5 **[0074]** Typically, a compound or composition of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be
10 combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations
15 contain from about 20% to about 80% active compound.

[0075] When the compositions of this invention comprise a combination of a compound of this invention and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should
20 be present at dosage levels of between about 10% to about 100%, and more preferably between about 10% to about 80% of the dosage normally administered in a monotherapy regime.

[0076] Upon improvement of a patient's condition, a
25 maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition
30 is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

-45-

[0077] As the skilled practitioner will appreciate, lower or higher doses than those recited above may be required. It should be understood that a specific dosage and treatment regimens for any particular patient will
5 depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the particular disease, the patient's disposition to
10 the disease being treated, and the judgment of the treating physician. The amount of active ingredients will also depend upon the particular compound and other therapeutic agent, if present, in the composition.

[0078] In a preferred embodiment, the invention
15 provides a method of treating a patient, preferably a mammal, having one of the aforementioned diseases, comprising the step of administering to said patient a compound or a pharmaceutically acceptable composition described above. In this embodiment, if the patient is
20 also administered another therapeutic agent or caspase inhibitor, it may be delivered together with the compound of this invention in a single dosage form, or, as a separate dosage form. When administered as a separate dosage form, the other caspase inhibitor or agent may be
25 administered prior to, at the same time as, or following administration of a pharmaceutically acceptable composition comprising a compound of this invention.

[0079] The compounds of this invention may also be incorporated into compositions for coating implantable
30 medical devices, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising

-46-

a compound of the present invention and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention and a carrier suitable for coating said implantable device.

0080] Another aspect of the invention relates to inhibiting caspase activity in a biological sample, which method comprises contacting said biological sample with a compound of formula I or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0081] Inhibition of caspase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[0082] The compounds of this invention are useful in methods for preserving cells, such as may be needed for an organ transplant or for preserving blood products. Similar uses for caspase inhibitors have been reported (Schierle et al., *Nature Medicine*, 5, 97 (1999)). The method involves treating the cells or tissue to be preserved with a solution comprising the caspase inhibitor. The amount of caspase inhibitor needed will depend on the effectiveness of the inhibitor for the given cell type and the length of time required to preserve the cells from apoptotic cell death.

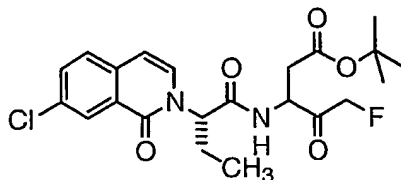
-47-

[0083] Nevertheless, the compounds of this invention are particularly suitable for methods involving inhibition of caspase activity in the central nervous system. Without being bound by theory, applicants' ester, amide-, and hydroxamide-containing prodrugs have the ability to pass through the blood brain barrier and into the central nervous system where the prodrug group is cleaved to provide an acid-containing drug. As would be recognized by a skilled practitioner, chemical compounds may be metabolized *in vivo* (i.e., at sites other than the prodrug cleavage site). Any such metabolites are included within the scope of this invention.

[0084] In order that this invention be more fully understood, the following preparative and testing examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

Example 1

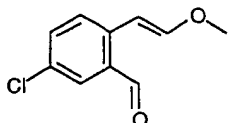
20 S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid tert butyl ester



25

Method A:

5-Chloro-2(2-methoxyvinyl)-benzoic acid



-48-

[0085] To a cooled (0°C) slurry of methoxymethyltriphenylphosphonium chloride (39g) in a mixture of diethyl ether (200ml) and *tert*-butanol (50ml) was added potassium *tert*-butoxide (12.8g) portionwise.

5 The resulting mixture was stirred at 0°C for 1 hour, then a solution of 2-formyl-5-chlorobenzoic acid (prepared as described in J. Org. Chem. 1996, 61, 3402) (10g) in diethyl ether (50ml) was added dropwise over 15 minutes. The resulting mixture was stirred for 1 hour at 0 °C,

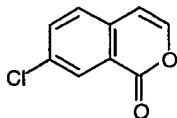
10 then warmed to ambient and stirred for an additional 90 minutes. The mixture was diluted with water (200ml) and the organic phase removed. The aqueous phase was acidified to pH1 with 1M HCl and extracted with ethyl acetate (3x50ml). The combined extracts were washed with

15 brine, dried (magnesium sulfate), filtered and concentrated. The residue was purified by flash chromatography (50% ethyl acetate/hexane) to afford the sub-title compound as a yellow solid (9.13g, 80%): ¹H NMR (400MHz, CDCl₃) δ 3.70-3.81 (3H, s), 6.20(0.3 H, d), 6.30 (0.3 H, d), 6.80(0.7 H, d), 7.01 (0.7 H, d), 7.30-8.15 (3H, m).

20

Method B:

7-Chloro-isochromen-1-one



25 [0086] Concentrated sulphuric acid (15ml) was added to 5-chloro-2(2-methoxyvinyl)-benzoic acid (4.43g) at 0 °C. The mixture was stirred for 2 hours, then diluted with ice/water. The product was extracted with ethyl acetate (3x15ml) and the combined extracts washed with saturated

30 sodium bicarbonate solution. The solution was dried

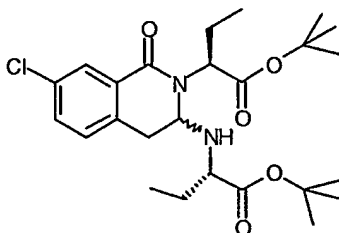
-49-

(magnesium sulfate), filtered and concentrated. The residue was purified by flash chromatography (0-5% ethyl acetate/hexane) to afford the sub-title compound as a white solid (3.04g, 81%); mp 109.8-110.9°C; ¹H NMR

5 (400MHz, CDCl₃) δ 6.51(1H, d), 7.28-7.32(1H, m), 7.41(1H, d), 7.64-7.70(1H, m), 8.28(1H, m).

Method C:

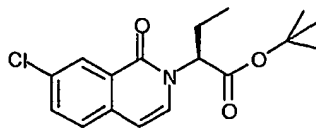
2-[3-(1-tertButoxycarbonyl-propylamino)-7-chloro-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl]-butyric acid tert-butyl
10 ester



[0087] A mixture of 7-Chloro-isochromen-1-one (10g) and (S)-2-aminobutyric acid, tert-butyl ester (22g) was heated at 85°C for 24 hours. The mixture was then cooled
15 and purified by flash chromatography (5-25% ethyl acetate/hexane) to afford the sub-title compound as a yellow oil (17.1g, 64%): ¹H NMR (400MHz, CDCl₃) δ 0.68-1.32 (6H, m), 1.50 (21H, m), 1.92 (1H, m), 2.15 (1H, m), 2.82-3.40 (3H, m), 4.41 (1H, m), 4.68 (1H, m), 7.11 (1H,
20 m), 7.35-7.52 (1H, m), 8.05 (1H, m).

Method D:

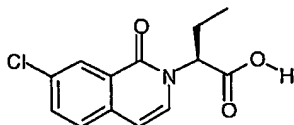
(S)-2-(7-Chloro-1-oxo-1H-isoquinolin-2-yl)-butyric acid,
tert butyl ester



25 **[0088]** To a stirred solution of 2-[3-(1-tertButoxycarbonyl-propylamino)-7-chloro-1-oxo-3,4-

-50-

dihydro-1*H*-isoquinolin-2-yl]-butyric acid *tert*-butyl ester (8.58g) in isopropanol (180ml) at 0°C was added concentrated hydrochloric acid (20ml). The resulting mixture was allowed to warm to ambient and stirred for 18
5 hours. The mixture was then diluted with ethyl acetate (500ml) and water (150ml). The organic phase was separated and washed with water, then brine, dried (magnesium sulfate), filtered and concentrated. The sub-
title product was obtained as a yellow solid (5.57g,
10 97%); m.p. 111.3-111.8°C; $[\alpha]_D^{25} -52.3^\circ$ ($c=1$, CHCl_3); IR (solid) 1731.4, 1649.5, 1593.2, 1229.6, 1152.8, 901.9 cm^{-1} ; ^1H NMR (400MHz, CDCl_3) δ 0.95 (3H, t), 1.48 (9H, s), 1.95 (1H, m), 2.30 (1H, m), 5.55 (1H, m), 6.40 (1H, m), 7.15 (1H, m), 7.49 (1H, m), 7.61 (1H, m), 8.40 (1H, m);
15 ^{13}C NMR (100MHz, CDCl_3) δ 10.9, 24.8, 28.1, 59.2, 82.8, 105.7, 127.3, 127.8, 128.1, 129.5, 133.1, 133.2, 135.4, 161.8, 170.2; MS ES(+) 322.4 (M+H).

Method E:(S)-2-(7-Chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyric acid

20

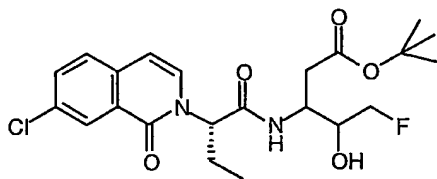
[0089] A solution of (S)-2-(7-Chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyric acid, *tert* butyl ester (322mg) in dichloromethane (14ml) was cooled to 0°C. Trifluoroacetic acid (3.5ml) was added and the resulting
25 mixture allowed to warm to room temperature and stir for 2 hours. The mixture was then concentrated under reduced pressure and the residue redissolved in dichloromethane. This process was repeated several times in order to remove excess trifluoroacetic acid. The resulting solid
30 was slurried in diethyl ether, filtered and washed with

-51-

more diethyl ether. The solid was then dried to constant weight under vacuum. This gave the sub-title product as a white solid (236mg, 89%); m.p. 159.6-160.1°C; $[\alpha]_D^{24}$ -47.0° (c=1.01, CHCl₃); ir (solid) 1731.4, 1639.3, 1577.8, 1209.1, 1168.1 cm⁻¹; ¹H NMR (400MHz, d₆-DMSO) δ 0.82 (3H, t), 2.00-2.25 (2H, m), 5.20 (1H, m), 6.70 (1H, d), 7.49 (1H, d), 7.70-7.81 (2H, m), 8.18 (1H, s); ¹³C NMR (100MHz, d₆-DMSO) δ 10.8, 22.7, 60.8, 104.9, 126.5, 126.6, 128.8, 131.6, 132.5, 133.1, 135.8, 160.5, 171.7; MS ES (+) 266.27 (M+H).

Method F:

3-[2-(7-Chloro-1-oxo-1H-isoquin-2-yl)-butyrylamino]-5-fluoro-4-hydroxy-pentanoic acid tert butyl ester

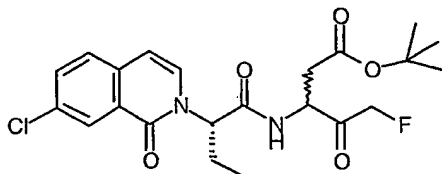


15 **[0090]** A stirred mixture of (S)-2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyric acid (15g), 3-amino-5-fluoro-4-hydroxy-pentanoic acid tert-butyl ester (prepared as described in *Tetrahedron Lett.* 1994, 35, 9693) (12.9g), HOBT (8.4g), DMAP (7.2g) and THF (450ml) was cooled to 20 0 °C then EDC (11.9g) was added. The mixture was allowed to warm to room temperature during 16h then concentrated under reduced pressure. The residue was purified by flash chromatography (30-60% ethyl acetate/hexane) to afford the subtitle compound as a white foam (24.6g, 25 96%); ¹H NMR (400MHz, CDCl₃) δ 0.92 (3H, m), 1.13-1.50 (9H, m), 1.95 (1H, m), 2.25 (1H, m), 2.45-2.78 (2H, m), 3.68-4.60 (5H, m), 5.50 (1H, m), 6.60 (1H, m), 7.21-7.60 (4H, m), 8.20-8.31 (1H, m); ¹⁹F NMR (376MHz, CDCl₃) (proton decoupled) δ -229.6, -229.7, -230.5, -230.6.

-52-

Method G:

3-[2-(7-Chloro-1-oxo-1*H*-isoquin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid *tert* butyl ester

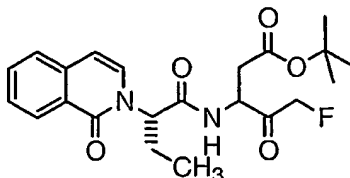


- 5 **[0091]** A stirred solution of 3-[2-(7-chloro-1-oxo-1*H*-isoquin-2-yl)-butyrylamino]-5-fluoro-4-hydroxy-pentanoic acid *tert* butyl ester (47.8g) in anhydrous DCM (1.2L) was treated with 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (53.5g) at 0°C. The resulting
- 10 mixture was kept at 0°C for 2hr, diluted with ethyl acetate, then poured into a 1:1 mixture of saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium thiosulfate. The organic layer was removed and the aqueous layer re-extracted with ethyl acetate. The
- 15 combined organic extracts were dried (Magnesium sulfate), filtered and concentrated. The residue was purified by flash chromatography (20-40% ethyl acetate/hexane) to afford the subtitle compound as a white solid (41.9g, 88%); ¹H NMR (400MHz, CDCl₃) δ 1.00 (3H, t), 1.29 (5H, s),
- 20 1.41 (4H, s), 2.01 (1H, m), 2.29 (1H, m), 2.61-3.05 (2H, m), 4.77 (3H, m), 5.50 (1H, m), 6.60 (1H, m), 7.20-7.34 (2H, m), 7.51 (1H, m), 7.62 (1H, m), 8.41 (1H, m); ¹⁹F NMR (376MHz, CDCl₃) (proton decoupled) δ -231.89, -232.30; ES(+) 453.1, ES(-) 451.1.

-53-

Example 2

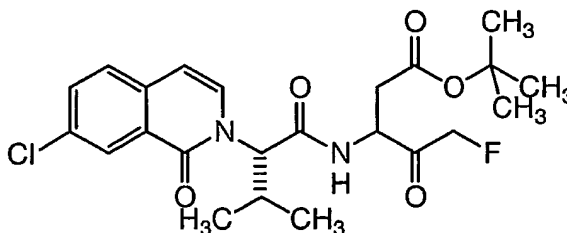
S-3-[2-(1-oxo-1*H*-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid *tert* butyl ester



5 **[0092]** This compound was prepared using methods similar to A-G and was isolated as a white foam.
 ^1H NMR (400MHz, CDCl_3) δ 1.10 (3H, m), 1.31 (5H, s), 1.45 (4H, s), 2.02 (1H, m), 2.31 (1H, m), 2.60-2.82 (1H, m), 2.88-3.08 (1H, m), 4.75-5.28 (3H, m), 5.51 (1H, m), 6.60
 10 (1H, m), 7.20-7.40 (2H, m), 7.60 (2H, m), 7.71 (1H, m), 8.42 (1H, m).; ^{19}F NMR (376MHz, CDCl_3) (proton decoupled) δ -232.0, -232.5; ES(+) 419.3, ES(-) 417.3.

Example 3

15 S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-3-methylbutyrylamino]-5-fluoro-4-oxo-pentanoic acid *tert* butyl ester

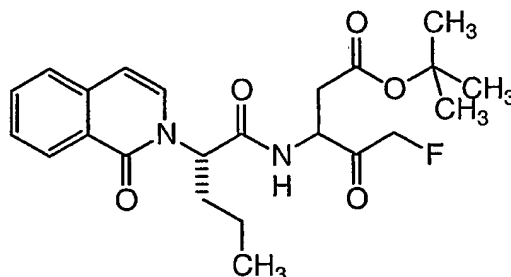


[0093] This compound was prepared using methods similar to A-G and was isolated as a white foam
 20 ^1H NMR (400MHz, CDCl_3) δ 0.83 (3H, m), 1.13 (3H, m), 1.30 (4.5H, s), 1.43 (4.5H, s), 2.55 (1H, m), 2.66-3.00 (2H, m), 4.74-5.30 (4H, m), 6.55 (1H, d), 7.32-7.62 (4H, m), 8.35 (1H, d); ^{19}F NMR (376MHz, CDCl_3) (proton decoupled) δ -231.5, -232.1; ES(+) 467.4.

-54-

Example 4

S-3-[2-(1-oxo-1*H*-isoquinolin-2-yl)-valeryl-amino]-5-fluoro-4-oxo-pentanoic acid tert butyl ester

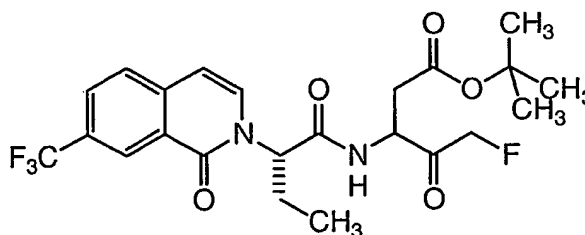


- 5 **[0094]** This compound was prepared using methods similar to A-G and was isolated as a white solid
- ^1H NMR (400MHz, CDCl_3) δ 1.01 (3H, m), 1.15-1.46 (11H, m), 1.98 (1H, m), 2.22 (1H, m), 2.60-3.04 (2H, m), 4.71-5.31 (3H, m), 5.61 (1H, m), 6.60 (1H, m), 7.18-7.30 (2H, m),
- 10 7.52 (2H, m), 7.70 (1H, m), 8.40 (1H, m); ^{19}F NMR (376MHz, CDCl_3) (proton decoupled) δ -232.0, -232.5; ES(+) 433.5, ES(-) 431.5.

Example 5

S-3-[2-(7-trifluoromethyl-1-oxo-1*H*-isoquinolin-2-yl)-butyryl-amino]-5-fluoro-4-oxo-pentanoic acid tert butyl ester

15



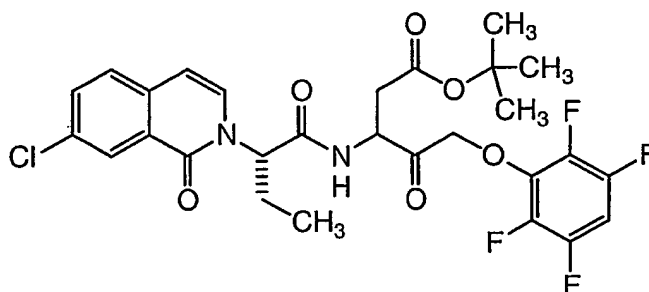
- [0095]** This compound was prepared using methods similar to A-G and was isolated as a white solid
- 20 ^1H NMR (400MHz, CDCl_3) δ 1.01 (3H, m), 1.20-1.40 (9H, 2s), 2.00 (1H, m), 2.30 (1H, m), 2.60-3.05 (2H, m), 4.75-5.26 (3H, m), 5.48 (1H, m), 6.62 (1H, m), 7.22 (1H, brs), 7.62 (1H, m), 7.65 (1H, m), 8.82 (1H, m), 8.65-8.72 (1H, m);

-55-

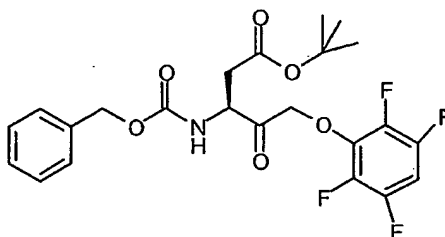
^{19}F NMR (376MHz, CDCl_3) (proton decoupled) δ -62.85, -62.88, -231.85, -232.20; ES(+) 487.5, ES(-) 485.5.

Example 6

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-
 5 butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid tert butyl ester

Method H:

(S)-3-Benzoyloxycarbonylamino-4-oxo-5-(2,3,5,6-
 10 tetrafluoro-phenoxy)-pentanoic acid tert-butyl ester



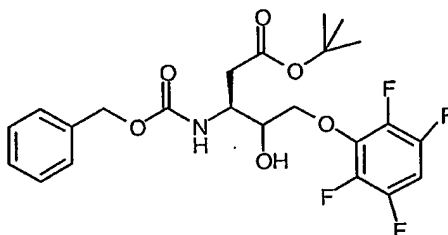
[0096] Potassium fluoride (2.8 g), was added
 portionwise to a stirred solution of (S)-3-
 15 benzyloxycarbonylamino-5-bromo-4-oxo-pentanoic acid tert-
 butyl ester (18.6 g) and 2,3,5,6-tetrafluorophenol (9.3
 g) in anhydrous DMF (250 mL) under nitrogen at room
 temperature. The mixture was then stirred for 18 hours
 before being quenched with ethyl acetate and water. The
 20 organic layer was removed and washed with sodium
 bicarbonate solution, dried (magnesium sulfate) and
 concentrated to give the sub-title product as an off-
 white solid (21.1 g, 96%); ^1H NMR (400 MHz, CDCl_3) δ 1.43

-56-

(9H, s), 2.76 (1H, dd), 3.06 (1H, dd), 4.67-4.71 (1H, m), 5.12 (1H, d), 5.22 (1H, d), 5.86 (1H, d), 7.35-7.38 (5H, m); ^{19}F NMR (376 MHz, CDCl_3) (proton decoupled) δ -139.98, -140.00, -140.04, -140.06, -157.05, -157.07, -157.11, -157.13; MS ES (+) 486.23 (M+H).

Method I:

(3S)-3-Benzoyloxycarbonylamino-4-hydroxy-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid tert-butyl ester



10

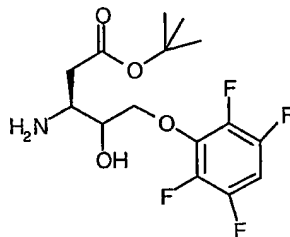
[0097] NaBH_4 (1.65 g) was added portionwise to a stirred solution of 3-benzoyloxycarbonylamino-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid tert-butyl ester (21.1 g) in anhydrous THF (220 mL) at -20°C under nitrogen. After stirring at this temperature for 3 hours, the reaction was quenched by the addition of saturated ammonium chloride solution and diluted with DCM. The organic layer was removed and the aqueous layer re-extracted with DCM. The combined organic extracts were washed with brine, dried (magnesium sulfate) and concentrated. The residue was purified by column chromatography (10%-20% ethyl acetate/hexane). The subtitle compound as a white solid (14.6 g, 73%); ^1H NMR (400 MHz, CDCl_3) δ 1.45 (9H, s), 2.61-2.77 (2H, m), 3.16-3.36 (1H, 2 x brd d), 4.12-4.22 (2H, m), 4.30-4.33 (1H, m), 5.44-5.69 (1H, 2 x d), 6.78-6.86 (1H, m), 7.35-7.36 (5H, m); ^{19}F NMR (346 MHz, CDCl_3) (proton decoupled) δ -139.87, -139.89, -139.93, -139.95, -139.98, -157.02, -157.05,

-57-

-157.06, -157.08, -157.09, -157.10, -157.12; ES (+)
488.27 (M+H).

Method J:

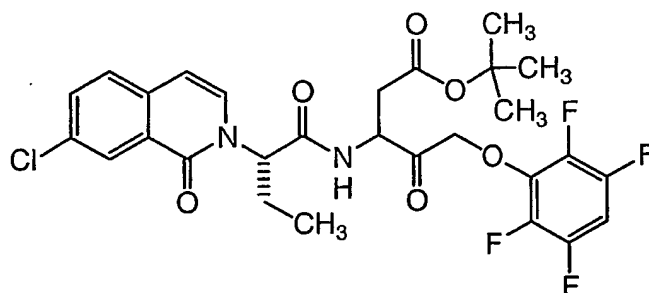
(3S)-3-Amino-4-hydroxy-5-(2,3,5,6-tetrafluoro-phenoxy)-
5 pentanoic acid tert-butyl ester



[0098] 10% Pd on carbon (2.92 g) was added portionwise to a solution of 3-benzyloxycarbonylamino-4-hydroxy-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid tert-butyl ester (14.6 g) in anhydrous MeOH (350 mL) which has been degassed under nitrogen (5x). The reaction was further degassed under nitrogen (3x) and hydrogen (5x) and stirred at room temperature for 20 minutes. The palladium residues were removed by filtration and the filtrate concentrated to give the sub-title compound as a white solid (9.5 g, 90%); ^1H NMR (400 MHz, CDCl_3) δ 1.49 (9H, s), 2.35-2.43 (1H, m), 5.67-5.64 (1H, m), 3.37-3.43 (1H, m), 3.77-3.87 (1H, m), 4.28-4.63 (2H, m), 6.77-6.86 (1H, m); ^{19}F NMR (346 MHz, CDCl_3) (proton decoupled) δ
20 -139.95, -139.97, -140.00, -140.03, -140.05, -140.08, -140.11, -140.13, -157.15, -157.18, -157.21, -157.23, -157.27, -157.29.

-58-

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid tert butyl ester



5 **[0099]** The titled compound was prepared using (S)-2-(7-Chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyric acid (prepared as described in methods A-E) and (3*S*)-3-Amino-4-hydroxy-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid tert-butyl ester (prepared as described in methods H-J)
 10 using procedures similar to those described in methods F-G. The product was isolated as a white solid.

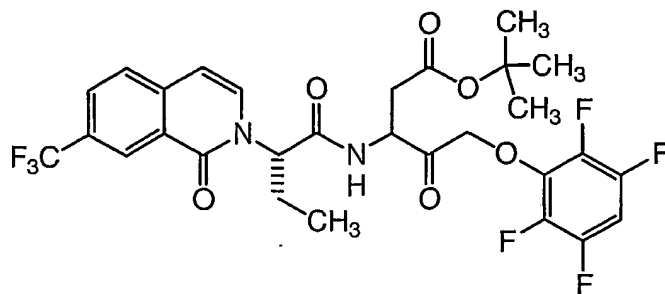
^1H NMR (400MHz, CDCl_3) δ 0.99 (3H, t), 1.33 (9H, s), 1.98-2.03 (1H, m), 2.26-2.33 (1H, m), 2.70 (1H, dd), 2.91 (1H, dd), 4.83-4.88 (1H, m), 5.05 (1H, d), 5.15 (1H, d), 5.47
 15 (1H, t), 6.57 (1H, d), 6.76-6.81 (1H, m), 7.25 (1H, d), 7.31 (1H, d), 7.49 (1H, d), 7.61 (1H, dd), 8.36 (1H, s); ^{19}F NMR (376MHz, CDCl_3) (proton decoupled) δ -139.86, -139.88, -139.92, -139.94, -157.09, -157.12, -157.15 and -157.17; ES(-) 597.3.

20

Example 7

S-3-[2-(7-trifluoromethyl-1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid

-59-



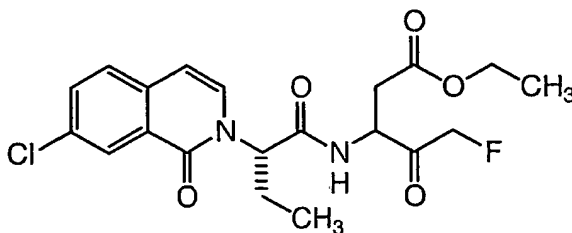
[0100] This compound was prepared using methods similar to A-G and was isolated as a white solid

¹H NMR (400MHz, CDCl₃) δ 1.00 (3H, t), 1.40 (9H, s), 2.00-2.50 (2H, 2m), 2.70-3.05 (2H, 2m), 4.95 (1H, m, CH), 5.10 (2H, dd), 5.55 (1H, t), 6.65 (1H, d), 6.80 (1H, m), 7.35 (1H, d), 7.65 (1H, d), 7.85 (1H, d), 8.70 (1H, s); ¹⁹F NMR (376MHz, CDCl₃) (proton decoupled) δ -62.88, -139.85, -157.13; ES(+) 633.3, ES(-) 631.3

10

Example 8

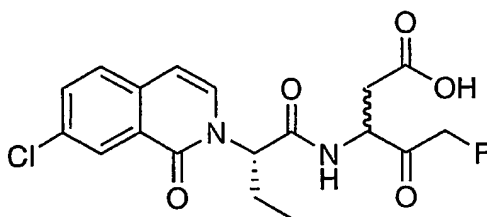
S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid ethyl ester



Method K:

15

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid



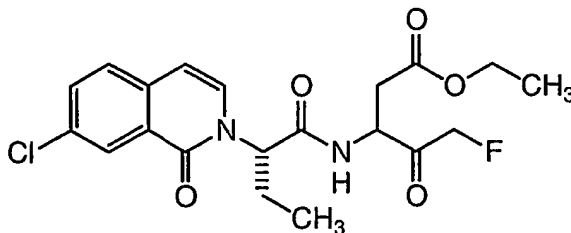
[0101] A solution of S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic

-60-

acid *tert* butyl ester (10 g) in dichloromethane (500 mL) was cooled to 0 °C. Trifluoroacetic acid (120 mL) was added portionwise and the resulting mixture was stirred at 0 °C for one hour and then allowed to warm to ambient temperature during two hours. The mixture was then concentrated under reduced pressure and the residue redissolved in dichloromethane. This process was repeated several times in order to remove excess trifluoroacetic acid. The solid was then dried to constant weight under vacuum. The product was isolated as a white solid (8.5 g, 97%); IR (solid) 1782.7, 1741.7, 1644.4, 1593.2, 1536.8, 1209.1, 1168.1, 1055.5, 840.4 cm⁻¹; ¹H NMR (400 MHz, d6-DMSO) δ 0.82 (3H, m), 1.81-2.25 (2H, m), 2.25-3.11 (2H, m), 4.15-5.60 (4H, m), 6.70 (1H, m), 7.55 (1H, m), 7.78 (2H, m), 8.15 (1H, s), 8.35-9.00 (1H, brm); ¹³C NMR (100 MHz, d6-DMSO) δ 10.6, 23.0, 24.0, 24.6, 32.9, 34.6, 34.7, 47.7, 52.2, 52.3, 58.2, 58.23, 58.7, 59.1, 83.4, 83.5, 85.2, 85.3, 103.9, 104.5, 104.7, 104.8, 126.5, 126.6, 128.8, 131.3, 131.4, 131., 133.1, 135.7, 135.73, 160.8, 170.2, 170.3, 170.4, 172.0, 173.1, 202.6, 202.7; ¹⁹F NMR (376 MHz, d6-DMSO) δ -226.70, -226.75, -227.51, -230.5, -231.16, -232.61, -232.67, -233.37; ES(+) 397.2, ES(-) 395.3.

Method L:

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid ethyl ester

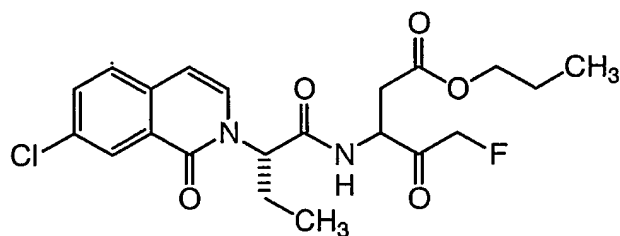


-61-

[0102] A solution of S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid (100 mg) in dichloromethane (1 mL) was cooled to 0 °C under nitrogen. N,N'-Carbonyldiimidazole (42 mg) was added in one portion and the reaction was stirred at 0 °C for 20 minutes, then allowed to warm to ambient temperature during 30 minutes. Ethanol (60 mg) in dichloromethane (0.2 mL) was added and the reaction stirred at ambient temperature for 18 hours then concentrated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate/hexane to 50% ethyl acetate/hexane) to afford the title compound as a viscous oil (65 mg, 61%); ¹H NMR (400 MHz, CDCl₃) δ 0.85-1.01 (3H, m), 1.05-1.30 (3H, m), 1.95 (1H, m), 2.25 (1H, m), 2.72-3.09 (2H, m), 3.90-4.18 (2H, m), 4.80-5.30 (3H, m), 5.56 (1H, m), 6.60 (1H, m), 7.15-7.85 (4H, m), 8.21 (1H, m); ¹⁹F (376 MHz, CDCl₃) δ -231.74, -232.08; ES(+) 425.2, ES(-) 423.3.

Example 9

20 S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid propyl ester



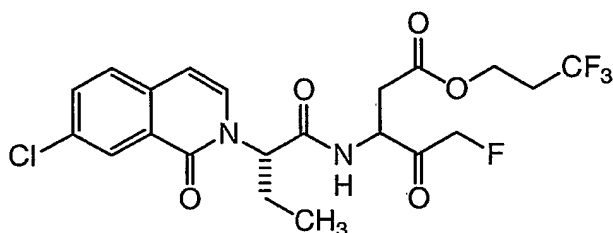
[0103] This was prepared using procedure similar to that described in Method L. The product was isolated as a viscous oil (51%); ¹H NMR (400 MHz, CDCl₃) δ 0.75-1.05 (6H, m), 1.35-1.65 (2H, m), 1.95 (1H, m), 2.25 (1H, m), 2.75-3.09 (2H, m), 3.80-4.05 (2H, m), 4.89-5.30 (3H, m), 5.52 (1H, m), 6.60 (1H, m), 7.15-7.80 (4H, m), 8.25 (1H,

-62-

m); ^{19}F NMR (376 MHz, CDCl_3) δ -231.74, -232.08; ES(+) 439.3, ES(-) 437.3.

Example 10

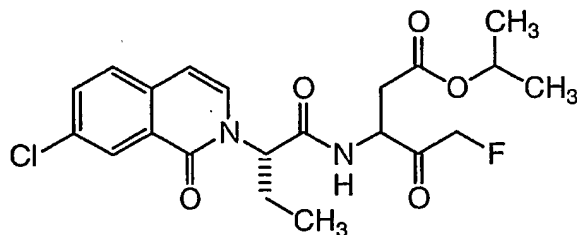
5 S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-5-fluoro-4-oxo-pentanoic acid 3,3,3-
trifluoro-propyl ester



[0104] This was prepared using procedure similar to that described in Method L. The product was isolated as
10 a viscous oil (32%); ^1H NMR (400 MHz, CDCl_3) δ 1.00 (3H, m), 1.98 (1H, m), 2.13-2.52 (3H, m), 2.80-3.09 (2H, m), 4.09-4.30 (2H, m), 4.75-5.21 (3H, m), 5.50 (1H, m), 6.61 (1H, m), 7.15-7.82 (4H, m), 8.26 (1H, m); ^{19}F NMR (376 MHz, CDCl_3) δ -231.76, -231.80, -65.49, -65.54; ES(+) 493.2, ES(-) 491.2.
15

Example 11

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-5-fluoro-4-oxo-pentanoic acid isopropyl
ester



20

[0105] This was prepared using procedure similar to that described in Method L. The product was isolated as a viscous oil (27%); ^1H NMR (400 MHz, CDCl_3) δ 1.02 (3H,

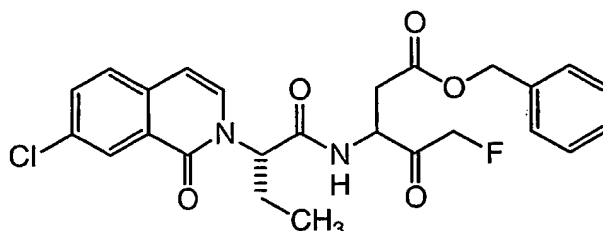
-63-

m), 1.05-1.35 (6H, m), 1.98 (1H, m), 2.25 (1H, m), 2.72-3.05 (2H, m), 4.75-5.30 (4H, m), 5.50 (1H, m), 6.60 (1H, m), 7.15-7.70 (4H, m), 8.25 (1H, m); ^{19}F (376 MHz, CDCl_3) δ -231.76, -232.12; ES(+) 439.2, ES(-) 437.3.

5

Example 12

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid benzyl ester

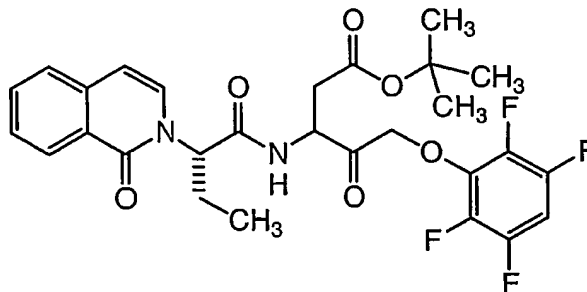


[0106] This was prepared using procedure similar to that described in Method L. The product was isolated as a viscous oil (53%); ^1H NMR (400 MHz, CDCl_3) δ 0.82-1.00 (3H, m), 1.95 (1H, m), 2.23 (1H, m), 2.82-3.09 (2H, m), 4.80-5.28 (5H, m), 5.55 (1H, m), 6.60 (1H, m), 7.15-7.60 (8H, m), 7.68-7.85 (1H, m), 8.20 (1H, m); ^{19}F NMR (376 MHz, CDCl_3) δ -231.62, -231.89; ES(+) 487.2, ES(-) 485.3.

15

Example 13

(S,S)-3-[2-(1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid tert butyl ester



20

[0107] This compound was prepared using (S)-2-(1-oxo-1H-isoquinolin-2-yl)-butyric acid (prepared from 2-formylbenzoic acid using procedures similar to those

-64-

described in methods A-E) and (3S)-3-Amino-4-hydroxy-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid *tert*-butyl ester (prepared as described in methods H-J) using procedures similar to those described in methods F-G.

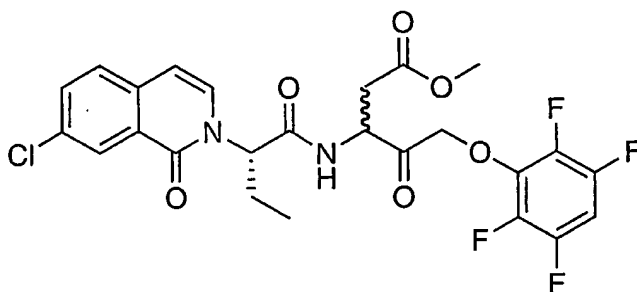
5 This compound was isolated as a white solid

This compound was prepared using methods similar to A-G and was isolated as a white solid

^1H NMR (400MHz, CDCl_3) δ 0.98 (3H, t), 1.30 (9H, s), 1.98-2.02 (1H, m), 2.26-2.32 (1H, m), 2.68 (1H, dd), 2.90 (1H, dd), 4.83-4.88 (1H, m), 5.06 (1H, d), 5.15 (1H, d), 5.50 (1H, t), 6.60 (1H, d), 6.75-6.82 (1H, m), 7.23 (1H, d), 7.33 (1H, d), 7.49-7.55 (1H, m), 7.68 (1H, t), 8.41 (1H, d); ^{19}F NMR (376MHz, CDCl_3) (proton decoupled) δ -139.94, -139.97, -140.0, -140.02, -157.06, -157.09, -157.12, -157.14; ; ES(+) 565.3, ES(-) 563.3.

Example 14

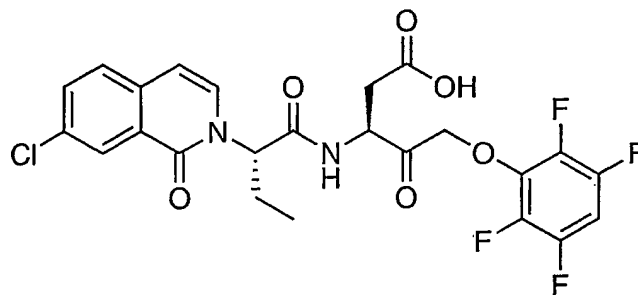
S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid methyl ester



Method M:

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid

-65-



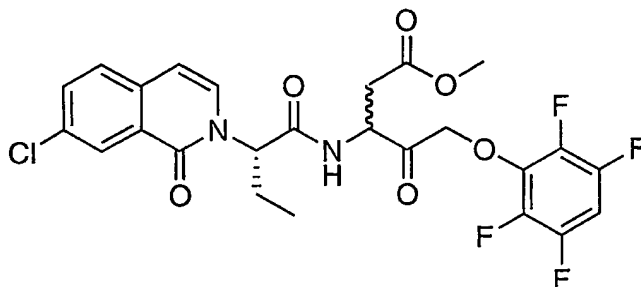
[0108] A solution of S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid *tert* butyl ester (7.4 g) in dichloromethane (100 mL) was cooled to 0°C. 50% Trifluoroacetic acid in dichloromethane (100 mL) was added and the resulting mixture stirred at 0 °C for one hour and then allowed to warm to ambient temperature during two hours. The mixture was then concentrated under reduced pressure and the residue redissolved in dichloromethane. This process was repeated several times in order to remove excess trifluoroacetic acid. The solid was then dried to constant weight under vacuum. The product was isolated as a white solid (6.1 g, 94%); IR (solid) 1639.3, 1618.8, 1593.2, 1516.4, 1485.6, 1219.4, 1168.1, 1106.7, 932.6, 830.2 cm⁻¹; ¹H NMR (400 MHz, d₆-DMSO) δ 0.80 (3H, t), 1.94-2.12 (2H, m), 2.55-2.61 (1H, m), 2.74-2.80 (1H, m), 4.58-4.63 (1H, m), 5.12-5.76 (3H, m), 6.70 (1H, d), 7.51-7.78 (4H, m), 8.11-8.12 (1H, m), 8.60-8.95 (1H, 3d); ¹³C NMR (100 MHz, d₆-DMSO) δ 23.85, 24.52, 32.99, 34.67, 47.87, 52.81, 55.26, 58.25, 58.91, 74.43, 75.65, 100.10, 100.34, 100.58, 101.05, 101.29, 104.65, 126.51, 136.61, 131.31, 131.40, 133.04, 135.64, 135.68, 139.03, 139.18, 141.47, 141.62, 144.68, 144.80, 144.90, 147.10, 147.19, 160.78, 170.45, 172.07, 173.02, 202.2; ¹⁹F NMR (376 MHz, d₆-DMSO) δ -140.57, -140.60, -140.64, -140.66, -141.00, -141.03, -141.06,

-66-

-141.09, -156.78, -156.80, -156.84, -156.86, -156.96,
-156.98, -157.02, -157.04; ES(+) 543.2, ES(-) 541.3.

Method N:

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-
5 butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid methyl ester



[0109] A solution of S-3-[2-(7-chloro-1-oxo-1H-
isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-
10 tetrafluoro-phenoxy)-pentanoic acid (100 mg) in
dichloromethane (1 mL) was cooled to 0 °C under nitrogen.
N,N'-Carbonyldiimidazole (35 mg) was added in one portion
and the reaction was stirred at 0 °C for 20 minutes, then
allowed to warm to ambient temperature during 30 minutes.
15 Methanol (29 mg) in dichloromethane (0.2 mL) was added
and the reaction stirred at room temperature for 18 hours
then concentrated *in vacuo*. The residue was purified by
column chromatography (20% ethyl acetate/hexane) to
afford the title compound as a white solid (42 mg, 41%);
20 IR (solid) 3294.6, 3075.4, 2946.7, 1731.6, 1641.1,
1622.0, 1588.7, 1512.4, 1483.8, 1436.2, 1369.5, 1331.3,
1274.2, 1217.0, 1169.3, 1102.6, 940.6, 902.5, 831.0,
783.4, 707.1, 688.1; ¹H NMR (400 MHz, CDCl₃) δ 0.96-1.00
(3H, m), 1.99-2.08 (1H, m), 2.25-2.32 (1H, m), 2.81-2.87
(1H, m), 2.97-3.15 (1H, 2dd), 3.57 & 3.70 (3H, 2s), 4.74-
25 5.10 (3H, m), 5.43-5.49 (1H, 2t), 6.58 (1H, 2d), 6.71-82
(1H, m), 7.25 (1H, 2d), 7.30-7.51 (2H, m), 7.62 (1H, 2d),

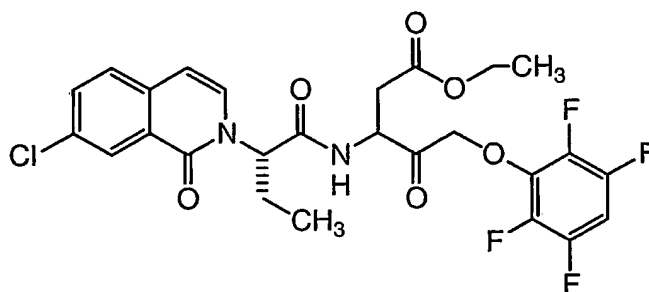
-67-

8.37 (1H, 2d); ^{19}F NMR (376 MHz, CDCl_3) δ -139.73, -139.75, -139.76, -139.79, -139.80, -139.81, -139.82, -157.12, -157.14, -157.18, -157.20, -157.23, -157.26, -157.29; ES(+) 557.2, ES(-) 555.3.

5

Example 15

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid ethyl ester

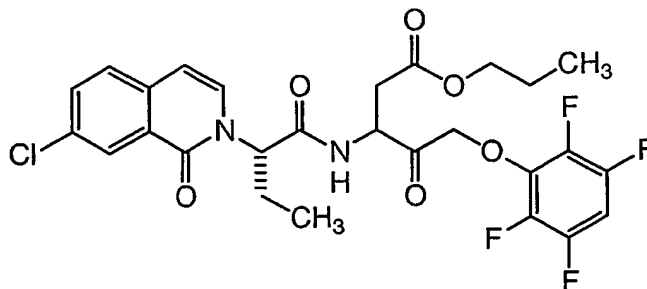


10 **[0110]** This was prepared from S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid using procedure similar to that described in Method N. The product was isolated as a white solid (41%); IR (solid) 3289.8, 3056.3, 2937.2, 1731.6, 1645.9, 1612.5, 1588.7, 1517.2, 1483.8, 1431.4, 1369.5, 1269.4, 1174.1, 1102.6, 1031.1, 940.6, 893.0, 831.0, 711.9, 683.3; ^1H NMR (400 MHz, CDCl_3) δ 0.96-1.01 (3H, m), 1.71 & 1.26 (3H, 2t), 1.92-2.08 (1H, m), 2.21-2.32 (1H, m), 2.79-2.83 (1H, m), 2.94-3.12 (1H, 2dd), 4.02 & 4.15 (2H, 2q), 4.72-5.06 (3H, m), 5.41-5.48 (1H, 2t), 6.58 (1H, 2d), 6.69-6.83 (1H, m), 7.24-7.31 (1.5 H, m), 7.46-7.51 (1.5H, m), 7.62 (1H, 2d), 8.37 (1H, 2d); ^{19}F NMR (376 MHz, CDCl_3) δ -139.75, -139.77, -139.80, -139.80, -139.83, -139.86, -157.08, -157.10, -157.14, -157.16, -157.18, -157.21, -157.24, -157.26; ES(+) 571.2, ES(-) 569.4.

-68-

Example 16

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid propyl ester



5

[0111] This was prepared from S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid using procedure similar to that described in Method N. The product was isolated as a white solid (74%); IR (solid) 3298.4, 2965.6, 2940.0, 2868.3, 1731.4, 1654.6, 1623.9, 1598.3, 1511.2, 1485.6, 1270.6, 1168.1, 1101.6, 937.7, 819.9, 717.5; ¹H NMR (400 MHz, CDCl₃) δ 0.84-1.00 (6H, m), 1.53-1.65 (2H, 2q), 1.95-2.03 (1H, m), 2.26-2.32 (1H, m), 2.79-2.84 (1H, m), 2.96-3.14 (1H, 2dd), 3.91 & 4.05 (2H, 2t), 4.75-5.12 (3H, m), 5.41-5.46 (1H, 2t), 6.58 (1H, 2d), 6.70-6.82 (1H, m), 7.25 (1H, 2d), 7.30-7.50 (2H, m), 7.62 (1H, 2d), 8.36 (1H, 2d); ¹⁹F NMR (376 MHz, CDCl₃) δ -139.76, -139.78, -139.80, -139.82, -139.84, -139.86, -157.06, -157.08, -157.12, -157.14, -157.17, -157.19, -157.23, -157.25; ES(+) 585.2, ES(-) 583.3.

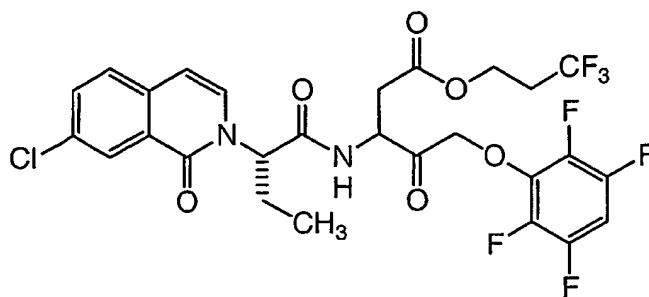
20

Example 17

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid 3,3,3-trifluoro-propyl ester

25

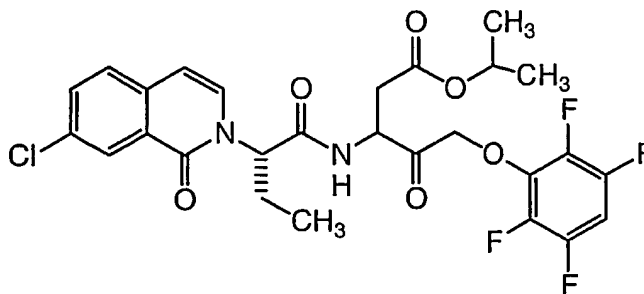
-69-



[0112] This was prepared from S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid using procedure
 5 similar to that described in Method N. The product was isolated as a white solid (39%); IR (solid) 3303.6, 2965.6, 2929.7, 1746.8, 1644.4, 1618.8, 1593.2, 1516.4, 1490.8, 1367.9, 1255.2, 1157.9, 1137.4, 1106.7, 1009.4, 942.8, 835.3, 712.4; ^1H NMR (400 MHz, CDCl_3) δ 0.96-1.01
 10 (3H, m), 1.93-2.01 (1H, m), 2.19-2.62 (3H, m), 2.84-2.90 (1H, m), 2.95-3.14 (1H, 2dd), 4.20 & 4.32 (2H, 2t), 4.72-5.09 (3H, m), 5.40-5.45 (1H, 2t), 6.58 (1H, 2d), 6.70-6.81 (1H, m), 7.25 (1H, 2d), 7.34-7.51 (2H, m), 7.62 (1H, 2d), 8.36 (1H, 2d); ^{19}F (376 MHz, CDCl_3) δ -64.49, -65.53,
 15 -139.67 -139.69, -139.73, -139.75; -157.17, -157.20, -157.23, -157.25, -157.28, -157.31, -157.33; ES(+) 639.4, ES(-) 637.6.

Example 18

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-
 20 butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
 pentanoic acid isopropyl ester

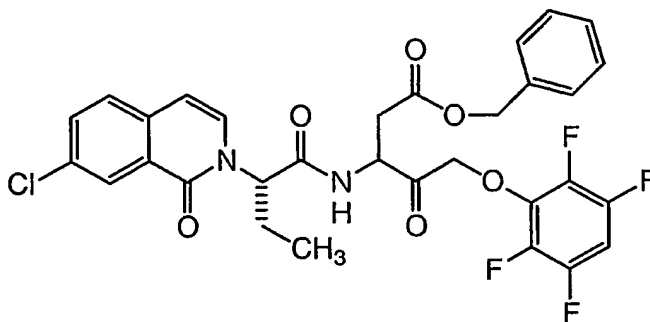


-70-

[0113] This was prepared from S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid using procedure similar to that described in Method N. The product was
5 isolated as a white solid (33%); IR (solid) 3283.1, 2980.9, 2929.7, 2878.5, 1731.4, 1654.6, 1618.8, 1598.3, 1511.2, 1485.6, 1373.0, 1332.0, 1275.7, 1214.2, 1173.3, 1111.8, 978.7, 937.7, 901.9, 825.0, 712.4; ¹H NMR (400 MHz, CDCl₃) δ 0.96-1.00 (3H, m), 1.13-1.17 (3H, m), 1.24
10 (3H, d), 1.98-2.06 (1H, m), 2.24-2.31 (1H, m), 2.73-2.78 (1H, m), 2.81-3.12 (1H, 2dd), 4.73-5.12 (4H, m), 5.41-5.47 (1H, dt), 6.58 (1H, 2d), 6.72-6.84 (1H, m), 7.25 (1H, 2d), 7.31-7.50 (2H, m), 7.62 (1H, 2d), 8.37 (1H, 2d); ¹⁹F NMR (376 MHz, CDCl₃) δ -139.75, -139.78, -139.80,
15 -139.81, -139.82, -139.84, -139.86, -139.88, -157.04, -157.06, -157.10, -157.12, -157.16, -157.18, -157.21, -157.24; ES(+) 585.2, ES(-) 583.3.

Example 19

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-
20 butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid benzyl ester



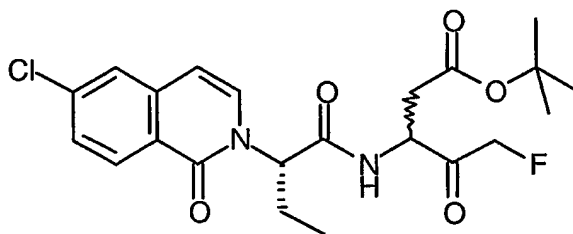
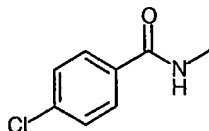
[0114] This was prepared from S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid using procedure similar to that described in Method N. The product was
25

-71-

isolated as a white solid (36%); IR (solid) 3285.1, 3061.1, 2951.5, 1736.4, 1650.6, 1626.8, 1593.4, 1512.4, 1488.6, 1388.3, 1280.8, 1174.1, 1102.6, 937.7, 835.3, 748.2; ^1H NMR (400 MHz, CDCl_3) δ 0.93-1.00 (3H, m), 1.93-2.02 (1H, m), 2.24-2.28 (1H, m), 2.86-2.92 (1H, m), 2.99-3.19 (1H, 2dd), 4.74-5.14 (5H, m), 5.40-5.44 (1H, 2t), 6.57 (1H, 2d), 6.70-6.84 (1H, m), 7.23 (1H, d), 7.34-7.49 (7H, m), 7.61-7.63 (1H, m), 8.38 (1H, 2d); ^{19}F (376 MHz, CDCl_3) δ -139.72, -139.74, -139.78, -139.81, -139.83, -157.06, -157.08, -157.12, -157.14, -157.18, -157.20, -157.23, -157.26; ES(+) 633.4, ES(-) 631.6.

Example 20

S-3-[2-(6-chloro-1-oxo-1H-isoquinolin-2-yl)-
butyrylamino]-5-fluoro-4-oxo-pentanoic acid tert-butyl
 15 ester

Method O:4-Chloro-N-methyl-benzamide

20

[0115] To a 0 °C solution of the 4-chlorobenzoyl chloride (4.50g) in dichloromethane (10mL) was added an 8M solution of methylamine in ethanol dropwise. The solution was stirred for 16 h and then evaporated to dryness. The residue was diluted with saturated sodium bicarbonate solution (10mL) and extracted three times

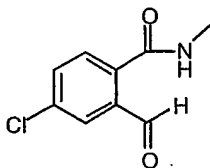
25

-72-

with ethyl acetate (3x20mL), the organics washed with
brine (10mL), dried (MgSO₄) and concentrated *in vacuo* to
afford the sub-title compound as a white solid (4.33g;
97%): ¹H NMR (400MHz, CDCl₃) δ 3.00 (3H, s), 7.40 (1H,
5 brs) 7.40 (1H, d), 7.70 (1H, d).

Method P:

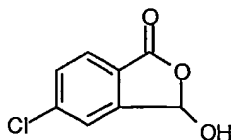
2-formyl-4-chloro-N-methylbenzamide



[0116] To a solution of 4-chloro-N-methyl-benzamide
10 (3.1g) in THF (30mL) was added *n*-butyl lithium (30.1mL of
2.5M hexane solution) and the solution refluxed for 45
min. The solution was then cooled to 0 °C and *N*-
methylformanilide (9.27mL) added dropwise over 2 min.
The solution was then refluxed for 2 h and then cooled to
15 ambient temperature, water (80mL) added and the solution
acidified to pH 1 with 2M HCl. The solution was then
extracted three times with ethyl acetate (3x50mL), washed
with brine (20mL), dried (MgSO₄) and concentrated *in*
vacuo. The resulting brown oil was purified on silica by
20 flash chromatography to afford the sub-titled product as
a pale yellow solid (2.13g; 59%); ¹H NMR (400MHz, CDCl₃) δ
2.90 (3H, s), 4.25 (1H, d) 5.60 (1H, d), 7.35 (2H, s),
7.60 (1H, s).

Method Q

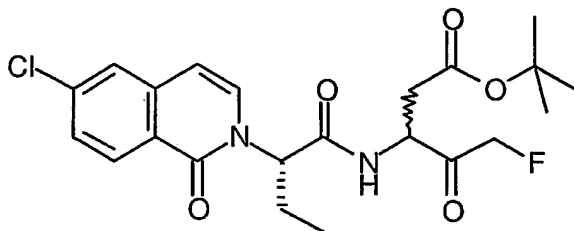
25 2-Formyl-4-chlorobenzoic acid



-73-

[0117] A mixture of 2-formyl-4-chloro-N-methylbenzamide (3.19g) and 10M hydrochloric acid (30ml) was heated at reflux for 18 hours. The mixture was cooled and basified with saturated sodium hydrogen carbonate solution. The solution was then washed with ethyl acetate, then acidified with 2M hydrochloric acid. The product was extracted with ethyl acetate and the combined extracts dried with magnesium sulfate. The solution was then filtered and concentrated. This furnished 2-formyl-4-chlorobenzoic acid as a yellow solid (2.22g, 75%); ¹H NMR (400MHz, CDCl₃) δ 6.65 (0.5H, brs), 7.50 (2H, m), 7.65 (1H, m), 7.85 (0.5H, brm), 8.05 (1H, m).

S-3-[2-(6-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-5-fluoro-4-oxo-pentanoic acid tert-butyl ester

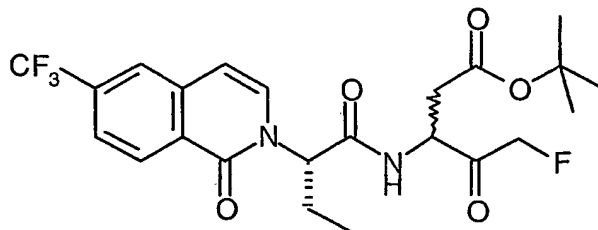


[0118] This was prepared from 2-formyl-4-chlorobenzoic acid (prepared as described in methods O-Q) using procedures similar to those described in methods A-G. The title compound was isolated by preparative HPLC and was obtained as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 0.97 (3H, m), 1.90-2.31 (2H, m), 2.65-3.30 (2H, m), 4.20-5.75 (4H, m), 6.65 (1H, m), 7.40-7.60 (3H, m), 8.29 (1H, m), 9.20 (1H, br); ¹⁹F NMR (376 MHz, CDCl₃) (proton decoupled) δ -229.80, -232.07, -232.43, -232.58, -232.78; MS ES (-) 395.26 (M-H).

-74-

Example 21

S-3-[2-(6-trifluoromethyl -1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-5-fluoro-4-oxo-pentanoic acid tert-butyl
ester



5

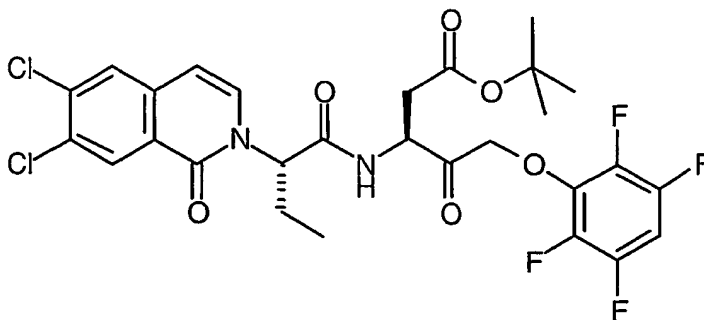
[0119] The above compound was prepared from 2-Formyl-4-trifluoromethylbenzoic acid (prepared from 4-trifluoromethylbenzoic acid using methods similar to those described in O-Q) using procedures similar to those described in methods A-G. The title compound was isolated as a white solid (95%, last step); ¹H NMR (400 MHz, CDCl₃) δ 0.99 (3H, m), 1.90-2.30 (2H, m), 2.60-3.50 (2H, m), 4.20-5.75 (4H, m), 6.80 (1H, m), 7.50-7.90 (3H, m), 7.92 (1H, m), 8.40-8.60 (1H, m); ¹⁹F NMR (376 MHz, d6-DMSO) (proton decoupled) δ -63.60, -63.61, -63.65, -231.67, -231.80, -232.06, -232.18; MS ES(+) 431.26 (M+H).

15

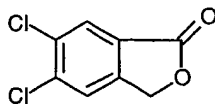
Example 22

(S,S)-3-[2-(6,7-dichloro-1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid tert-butyl ester

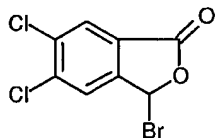
20



-75-

Method R:5,6-Dichloro-3H-isobenzofuran-1-one

[0120] NaBH₄ (5.2 g) was added to a stirred solution of
5 4,5-dichlorophthalic anhydride (20 g) in anhydrous DMF
(100 mL) at 0 °C under nitrogen in small portions over 1
hour. The reaction was warmed to room temperature for a
further 2 hours and poured into ice/1M HCl. The
resultant white precipitate (4,5-dichloro-2-
10 hydroxymethyl-benzoic acid) was collected by filtration
and dried under vacuum. The precipitate was suspended in
toluene (200 mL) with catalytic pTSA and heated to reflux
under Dean-Stark conditions (precipitate dissolves on
heating) for 18 hours. The reaction was cooled to room
15 temperature and the resultant white precipitate collected
by filtration to give the sub-title compound as a white
solid (14.0 g, 75%); ¹H NMR (400 MHz, d₆-DMSO) δ 5.40 (2H,
s), 8.05 (1H, s), 8.15 (1H, s).

Method S:20 3-Bromo-5,6-Dichloro-3H-isobenzofuran-1-one

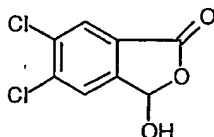
[0121] A suspension of 5,6-Dichloro-3H-isobenzofuran-
1-one (1.45 g), N-bromosuccinimide (1.27 g) and catalytic
benzoyl peroxide in chloroform (30 mL) was heated to
25 reflux for 1 hour. After cooling, the reaction mixture
was washed with water, brine, dried (magnesium sulfate),
filtered and concentrated to give the sub-title compound

-76-

as a white solid (1.82 g, 91%); ^1H NMR (400 MHz, CDCl_3) δ 7.36 (1H, s), 7.77 (1H, s), 8.03 (1H, s).

Method T:

4,5-Dichloro-2-formyl-benzoic acid



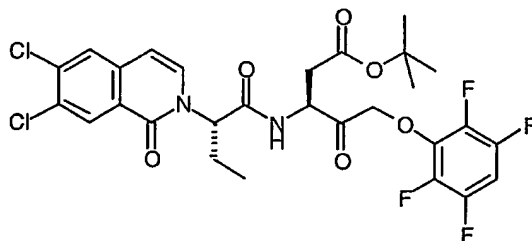
5

[0122] A suspension of 3-bromo-5,6-dichloro-3H-isobenzofuran-1-one (2.0 g) in 5% aqueous HCl (10 mL) and 80% aqueous dioxane (25 mL) were heated to reflux for 2 hours. The solvent was removed and the resulting residue re-dissolved in ethyl acetate, dried (magnesium sulfate) and concentrated. The resultant yellow solid was recrystallized from DCM/hexane to give the sub-title compound as a white solid (1.13 g, 73%); ^1H NMR (400 MHz, CDCl_3) δ 6.66 (0.84H, s), 7.95 (0.16H, s), 8.05 (0.84H), 8.12 (0.16H, s), 8.14 (0.84H, s), 8.41 (0.84H), 10.41 (0.16H, s), 11.07 (0.16 H, brs).

10

15

(S,S)-3-[2-(6,7-dichloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid tert-butyl ester



20

[0123] This compound was prepared using (S)-2-(6,7-dichloro-1-oxo-1H-isoquinolin-2-yl)-butyric acid (synthesized from 4,5-dichloro-2-formyl-benzoic acid [prepared as described in methods R-T] using procedures similar to those described in methods A-E) and (3S)-3-Amino-4-hydroxy-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic

25

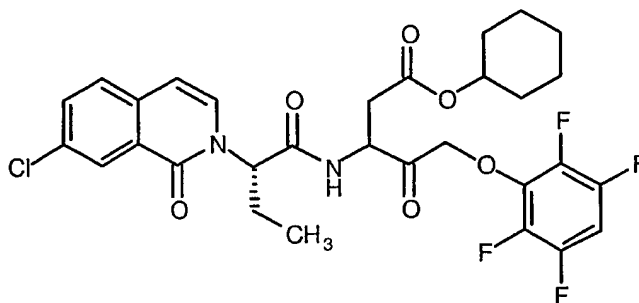
-77-

acid *tert*-butyl ester (prepared as described in methods H-J) using procedures similar to those described in methods F-G. The title compound was isolated as a white solid (94% last step); IR (solid) 1784.5, 1734.7, 1650.1, 1610.2, 1585.4, 1515.7, 1490.8, 1426.0, 1216.9, 1172.1, 1092.5, 933.1 cm^{-1} ; ^1H NMR (400 MHz, d_6 -DMSO) δ 0.80 (3H, t), 1.90-1.98 (1H, m), 2.04-2.12 (1H, m), 2.55-2.79 (2H, m), 4.56-4.71 (1H, m), 5.08-5.41 (3H, m), 6.67 (1H, d), 7.56-7.59 (2H, m), 8.07 (1H, brs), 8.25 (1H, d), 8.85-8.95 (1H, 2 x d), 12.73 (1H, brs); ^{19}F NMR (376 MHz, d_6 -DMSO) (proton decoupled) δ -140.93, -140.95, -140.99, -141.01, -141.04, -141.07, -141.10, -156.76, -156.79, -156.82, -156.85, -156.89, -156.91; MS ES (+): 577.14 (M+H).

15

Example 23

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid cyclohexyl ester



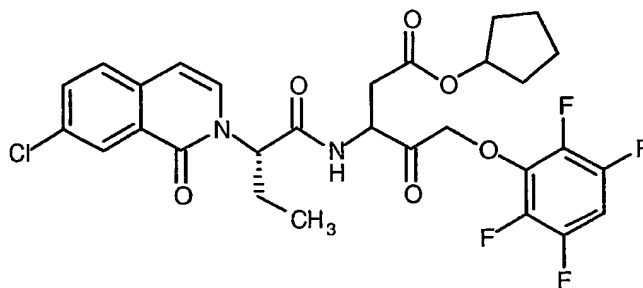
20 **[0124]** This was prepared using procedures similar to that described in Method N. The product was isolated as a white solid (24%); IR (solid) 1639, 1586, 1518, 1485, 832; ^1H NMR (400 MHz, CDCl_3) δ 0.96-1.00 (3H, m), 1.22-1.37 (6H, m), 1.51-1.55 (1H, m), 1.66-1.72 (3H, m), 1.90-1.95 (1H, m), 2.00 (1H, dd), 2.26-2.34 (1H, m), 2.79 (1H, 2dd), 3.03 (1H, 2dd), 4.73-5.11 (2H, 2dd), 4.89-4.94 (1H,

-78-

m), 5.45 (1H, dd), 6.57-6.60 (1H, m), 6.71-6.81 (1H, m),
 7.24 (1H, d), 7.42-7.50 (2H, m), 7.62 (1H, dd), 8.39
 (1H, dd); ^{19}F (376 MHz, CDCl_3) δ -139.74, -139.76,
 -139.79, -139.80, -139.82, -139.84, -156.96, -156.98,
 5 -157.01, -157.04, -157.09, -157.11, -157.15, -157.17;
 ES(+) 625.1, ES (-) 623.3.

Example 24

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-
butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
 10 pentanoic acid cyclopentyl ester

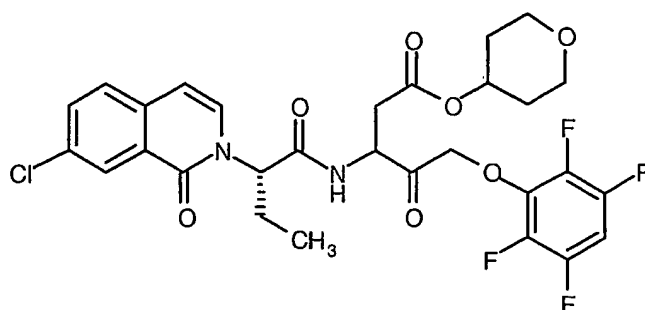


[0125] This was prepared using procedures similar to
 that described in Method N. The product was isolated as
 a white solid (40%); IR (solid) 1639, 1509, 1485, 841; ^1H
 15 NMR (400 MHz, CDCl_3) δ 0.96-1.01 (3H, m), 1.56-1.89
 (9H, m), 1.97-2.02 (1H, m), 2.27-2.32 (1H, m), 2.76 (1H,
 2dd), 3.02 (1H, 2dd), 4.74-5.16 (2H, 2dd), 4.88-4.92 (1H,
 m), 5.44 (1H, dd), 6.57 (1H, dd), 6.70-6.82 (1H, m), 7.26
 (1H, d), 7.41-7.52 (2H, m), 7.73 (1H, dd), 8.37 (1H, dd);
 20 ^{19}F (376 MHz, CDCl_3) δ -139.75, -139.77, -139.80, -139.83,
 -139.86, -157.01, -157.03, -157.07, -157.09, 157.13,
 -157.15, -157.19, -157.21; ES(+) 611.1, ES(-) 609.2.

Example 25

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-
 25 butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid tetrahydro-4H-pyran-4-ol ester

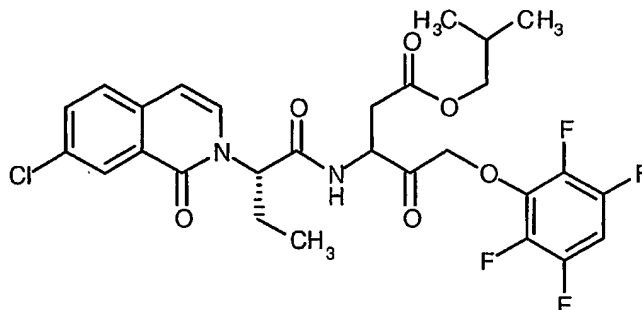
-79-



[0126] This was prepared using procedures similar to that described in Method N. The product was isolated as a white solid (41%); IR (solid) 1644, 1509, 1485, 827; ¹H NMR (400 MHz, CDCl₃) δ 0.96-1.01 (3H, m), 1.43-1.91 (4H, m), 1.95-2.03 (1H, m), 2.27-2.35 (1H, m), 2.84 (1H, 2dd), 3.03 (1H, 2dd), 3.41-3.54 (2H, m), 3.78-3.94 (2H, m), 4.77-5.11 (4H, 3m), 5.44 (1H, dd), 6.59 (1H, dd), 6.72-6.85 (1H, m), 7.25 (1H, d), 7.32-7.51 (2H, m), 7.63 (1H, dd), 8.35 (1H, dd); ¹⁹F (376 MHz, CDCl₃) δ -139.68, -139.69, -139.70, -139.72, -139.73, -139.75, -139.76, -157.06, -157.08, -157.12, -157.14, -157.17, -157.19, -157.22, -157.25; ES (+) 627.2, ES(-) 625.3.

Example 26

15 S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-pentanoic acid isobutyl ester



[0127] This was prepared using procedures similar to that described in Method N. The product was isolated as a white solid (72%); IR (solid) 1644, 1509, 1489, 832; ¹H

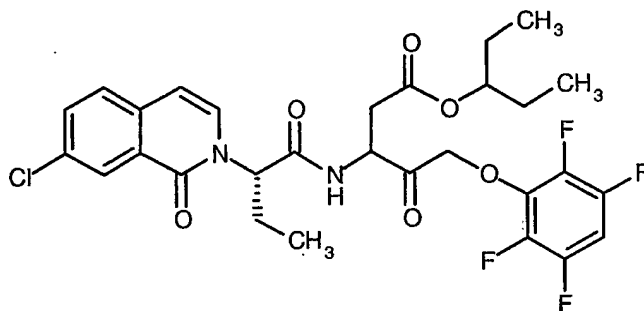
-80-

NMR (400 MHz, CDCl₃) δ 0.84-0.91 (6H, 2dd), 0.92-1.00 (3H, m), 1.79-2.02 (2H, m), 2.25-2.33 (1H, m), 2.80-2.91 (1H, m), 3.03 (1H, 2dd), 3.73 & 3.87 (2H, 2d), 4.74-5.10 (3H, m), 5.43-5.47 (1H, m), 6.57-6.59 (1H, m), 7.69-7.81 (1H, m), 7.24 (1H, d), 7.44-7.51 (2H, m), 7.62 (1H, dd), 8.39 (1H, dd); ¹⁹F (376 MHz, CDCl₃) δ -139.75, -139.78, -139.80, -139.81, -139.83, -139.83, -139.85, -157.04, -157.06, -157.10, -157.12, -157.16, -157.18, -157.22, -157.24; ES(+) 599.2, ES(-) 597.3.

10

Example 27

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid 3-pentanol ester

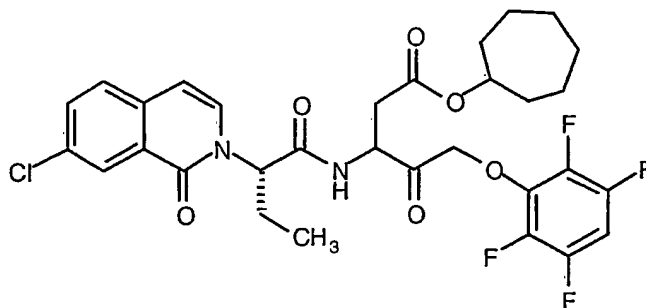


15 **[0128]** This was prepared using procedures similar to that described in Method N. The product was isolated as a white solid (23%); IR (solid) 1644, 1601, 1518, 1485, 832; ¹H NMR (400 MHz, CDCl₃) δ 0.77-0.89 (6H, m), 0.96-0.99 (3H, m), 1.41-1.55 (4H, m), 1.97-2.03 (1H, m), 2.26-2.34 (1H, m), 2.81 (1H, 2dd), 3.04 (1H, 2dd), 4.75-5.12 (4H, m), 5.43-5.46 (1H, m), 6.56-6.59 (1H, m), 7.71-7.84 (1H, m), 7.24 (1H, d), 7.32-7.51 (2H, m), 7.61-7.63 (1H, m), 8.37 (1H, dd); ¹⁹F (376 MHz, CDCl₃) δ -139.80, -139.80, -139.82, -139.84, -139.86, -139.88, -139.89, -139.92, -157.02, -157.05, -157.08, -157.10, -157.13, -157.15, -157.18, -157.21; ES(+) 613.1, ES(-) 611.3.

-81-

Example 28

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid cycloheptanol ester



5

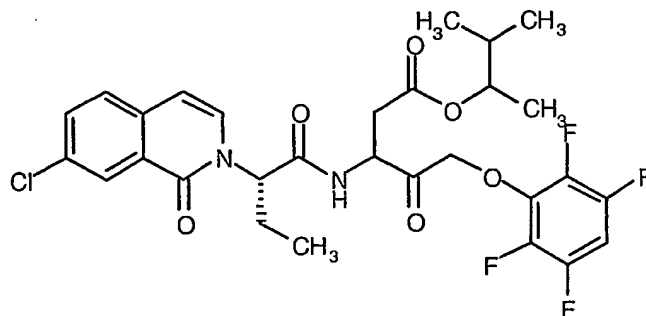
[0129] This was prepared using procedures similar to that described in Method N. The product was isolated as a white solid (11%); IR (solid) 2936, 1645, 1509, 1489, 1093, 939, 827; ¹H NMR (400 MHz, CDCl₃) δ 0.96-1.00 (3H, m), 1.42-1.60 (11H, m), 1.68-1.81 (1H, m), 1.82-1.91 (1H, m), 1.95-2.04 (1H, m), 2.26-2.33 (1H, m), 2.77 (1H, m), 3.03 (1H, m), 4.74-4.93 (2H, 2m), 5.09 (1H, dd), 5.45 (1H, dd), 6.57-6.59 (1H, m), 6.71-6.83 (1H, m), 7.24-7.26 (1H, m), 7.31-7.45 (1H, m), 7.48-7.50 (1H, m), 7.60-7.64 (1H, m), 8.38 (1H, dd); ¹⁹F (376 MHz, CDCl₃) δ -139.33, -139.36, -139.39, -139.42, -139.76, -139.78, -139.80, -139.81, -139.83, -139.86, -156.64, -156.66, -156.69, -156.71, -156.97, -157.00, -157.03, -157.05, -157.06, -157.10, -157.12, -157.15, -157.18; ES(+) 639.2, ES(-) 637.3.

20

Example 29

S-3-[2-(7-chloro-1-oxo-1*H*-isoquinolin-2-yl)-
butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-
pentanoic acid 2-hydroxy-3-methylbutanol ester

-82-

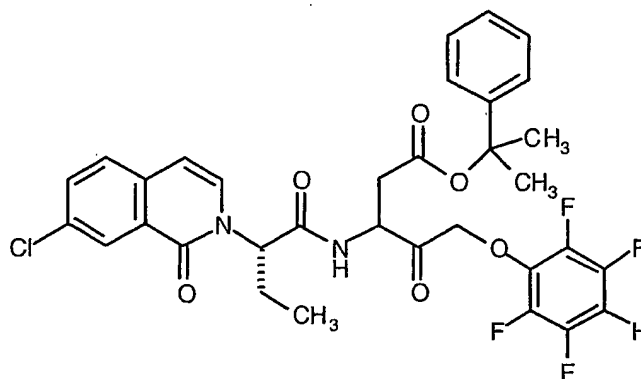


[0130] This was prepared using procedures similar to that described in Method N. The product was isolated as a white solid (24%); IR (solid) 1731, 1649, 1591, 1514,
 5 1485, 1098, 929, 827; ^1H NMR (400 MHz, CDCl_3) δ 0.80 (3H, d), 0.88 (3H, d), 0.96-1.00 (3H, m), 1.07-1.17 (3H, m), 1.63-1.71 (1H, m), 1.97-2.03 (1H, m), 2.25-2.32 (1H, m), 2.75-2.87 (1H, m), 2.93-3.12 (1H, m), 4.63-4.95 (3H, m), 5.08 (1H, dd), 5.42-5.46 (1H, m), 6.56-6.59 (1H, m),
 10 6.68-6.82 (1H, m), 7.30 (1H, 2d), 7.41-7.55 (1H, m), 7.63 (1H, d), 8.36 (1H, m); ^{19}F (376 MHz, CDCl_3) δ -139.39, -139.41, -139.43, -139.45, -139.77, -139.79, -139.82, -139.85, -139.87, -156.67, -156.69, -156.71, -156.74, -157.03, -157.05, -157.09, 157.11, -157.14, -157.16,
 15 -157.20, -157.22; ES(+) 613.3, ES(-) 611.3.

Example 30

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid 2-phenyl-2-methylpropanol ester

-83-

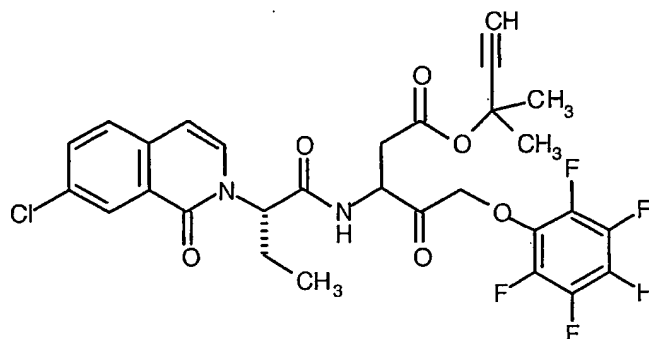
Method U

[0131] To a solution of S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid (100mg) in dichloromethane (1 mL) was added a solution of 2-phenylpropan-2-yl 2,2,2-trichloroacetimidate (prepared as described in Tetrahedron Letters 1993, **34**, 323-326) (103 mg) in cyclohexane (2ml). The resulting mixture was stirred at room temperature for 3 days, then concentrated *in vacuo*. The residue was purified by column chromatography (25% ethyl acetate/hexane). The compound was further purified by slurrying in cyclohexane/dichloromethane. This afforded the title compound as a white solid (65mg, 53%); IR (solid) 1731, 1690, 1654, 1516, 1485; ¹H NMR (400 MHz, CDCl₃) δ 1.01 (3H, t), 1.68 (6H, ds), 1.99 (1H, m), 2.25 (1H, m), 2.82 (1H, dd), 3.05 (1H, dd), 4.85 (1H, m), 5.00 (2H, m), 5.42 (1H, m), 6.56 (1H, d), 6.80 (1H, m), 7.19-7.35 (7H, m), 7.49 (1H, m), 7.61 (1H, m), 8.38 (1H, m); ES(+) 661.33, ES(-) 659.33.

Example 31

S-3-[2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid 2-methyl-3-butyn-2-ol ester

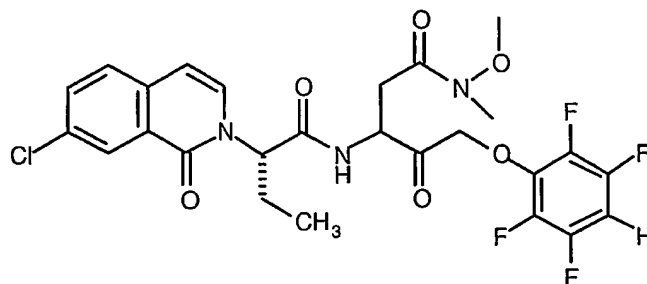
-84-



[0132] This was prepared using procedures similar to that described in Method U (Catalytic boron trifluoride diethyl ether complex was added to the reaction mixture, 1,1-dimethylpropionyl 2,2,2-trichloroacetimidate was prepared as described in J. Org. Chem. 2001, **66**, 7568). The product was isolated as a white solid (30%); ^1H NMR (400 MHz, CDCl_3) δ 1.00 (3H, m), 1.60 (6H, s), 2.01 (1H, m), 2.30 (1H, m), 2.50 (0.77H, s), 2.59 (0.23H, s), 2.77-3.14 (2H, m), 4.75-5.20 (3H, m), 5.51 (1H, m), 6.60 (1H, d), 6.80 (1H, m), 7.20-7.40 (2H, m), 7.50 (1H, d), 7.65 (1H, d), 8.40 (1H, s); ^{19}F (376 MHz, CDCl_3) δ -139.76, -139.79, -139.81, -139.82, -139.83, -139.86, -139.89, -157.03, -157.05, -157.09, -157.11, -157.13, -157.16, -157.19, -157.22; ES(+) 609.29, ES(-) 607.26.

Example 32

(S)-3-[2-(7-Chloro-1-oxo-1H-isoquinolin-2-yl)-butyrylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid methoxy-methyl-amide



-85-

[0133] This was prepared using procedures similar to that described in Method N. The product was isolated as a white solid (67%); IR (solid) 2970, 1645, 1514, 1495, 1093, 997, 943, 836; ¹H NMR (400 MHz, CDCl₃) δ 0.95-1.03 (3H, m), 1.94-2.03 (1H, m), 2.21-2.32 (1H, m), 2.85 (1H, dd), 3.05 & 3.16 (3H, 2 x s), 3.32 (1H, m), 3.61 & 3.72 (3H, 2s), 4.73-4.98 (2H, 2m), 5.18 (1H, dd), 5.40-5.49 (1H, m), 6.56-6.59 (1H, m), 6.69-6.81 (1H, m), 7.36-7.62 (4H, m), 8.37 (1H, dd); ¹⁹F (376 MHz, CDCl₃) δ -139.99, -140.01, -140.03, -140.04, -140.06, -140.09, -156.94, -156.96, -156.99, -157.02, -157.08, -157.01, -157.13, -157.16; ES(+) 586.2, ES(-) 584.2.

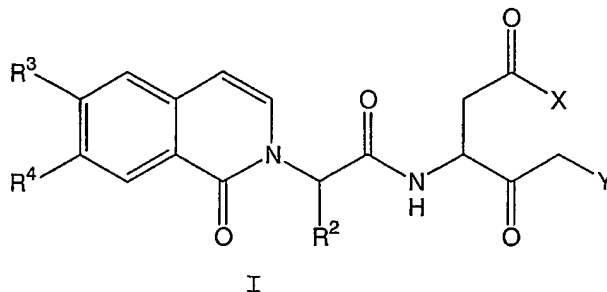
[0134] The documents cited herein are hereby incorporated by reference.

15 [0135] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments which utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention
20 is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example above.

-86-

We claim:

1. A compound of formula I:



5 wherein:

X is $-OR^1$ or $-N(R^5)_2$,

Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R^1 is:

10 C_{1-6} straight chained or branched alkyl,
alkenyl, or alkynyl, wherein the alkyl, alkenyl, or
alkynyl is optionally substituted with aryl, CF_3 , Cl, F,
OMe, OEt, OCF_3 , CN, or NMe_2 ;

C_{1-6} cycloalkyl, wherein 1-2 carbon atoms in the
cycloalkyl is optionally replaced with $-O-$ or $-NR^5-$;

15 R^2 is C_{1-6} straight chained or branched alkyl;

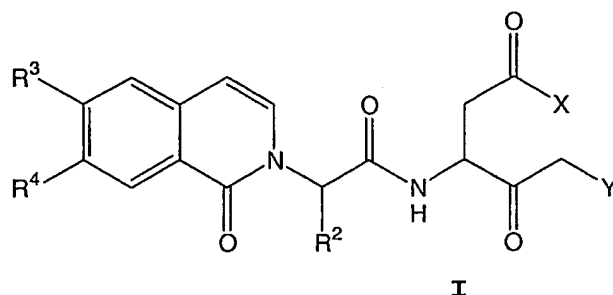
R^3 is hydrogen, halo, OCF_3 , CN, or CF_3 ;

R^4 is hydrogen, halo, OCF_3 , CN, or CF_3 ; and

20 each R^5 is independently H, C_{1-6} straight chained or
branched alkyl, aryl, $-O-C_{1-6}$ straight chained or branched
alkyl, or $-O$ -aryl.

-87-

2. A compound of formula I:



wherein:

- 5 X is $-OR^1$ or $-N(R^5)_2$,
 Y is halo, trifluorophenoxy, or tetrafluorophenoxy;
 R^1 is:
 C_{1-6} straight chained or branched alkyl,
 alkenyl, or alkynyl, wherein the alkyl, alkenyl, or
 10 alkynyl is optionally substituted with optionally
 substituted aryl, CF_3 , Cl, F, OMe, OEt, OCF_3 , CN, or NMe_2 ;
 C_{1-6} cycloalkyl, wherein 1-2 carbon atoms in the
 cycloalkyl is optionally replaced with $-O-$ or $-NR^5-$;
 R^2 is C_{1-6} straight chained or branched alkyl;
 15 R^3 is hydrogen, halo, OCF_3 , CN, or CF_3 ;
 R^4 is hydrogen, halo, OCF_3 , CN, or CF_3 ; and
 R^5 is H, C_{1-6} straight chained or branched alkyl, or
 $-O-C_{1-6}$ straight chained or branched alkyl; provided that
 if:
 20 Y is F;
 R^2 is isopropyl, R^3 is hydrogen, and R^4 is Cl; or
 R^2 is ethyl, R^3 is hydrogen, and R^4 is Cl or CF_3 ; or
 R^2 is ethyl, R^3 is Cl or CF_3 , and R^4 is hydrogen; then
 R^1 is not t-butyl; and if
 25 Y is 2,3,5,6-tetrafluorophenoxy;
 R^2 is ethyl; and
 R^3 and R^4 are each hydrogen; or

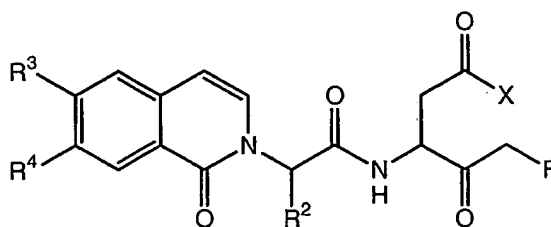
-88-

R^3 is hydrogen and R^4 is Cl or CF_3 ; or
 R^3 and R^4 are each Cl; then
 R^1 is not t-butyl.

5 3. The compound according to claim 1 or
 claim 2, wherein R^2 is ethyl, n-propyl, or isopropyl.

 4. The compound according to any one of claims
 1-3, wherein Y is F, trifluorophenoxy, or
 10 tetrafluorophenoxy.

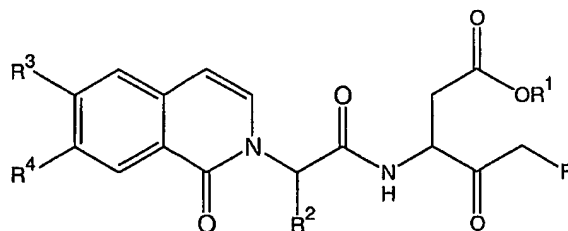
 5. The compound according to claims 1 or 2,
 having formula IA':



15

R^2 is ethyl, n-propyl, or isopropyl;
 R^3 is hydrogen, halo, OCF_3 , CN, or CF_3 ; and
 R^4 is hydrogen, halo, OCF_3 , CN, or CF_3 .

20 6. The compound according to claims 1 or 2,
 having formula IA:



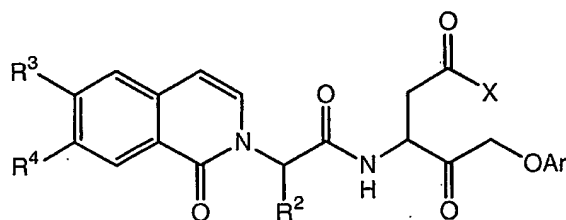
R^1 is C_{1-6} straight chained or branched alkyl
 optionally substituted with phenyl or CF_3 ;

25 R^2 is ethyl, n-propyl, or isopropyl;

-89-

R^3 is hydrogen, halo, OCF_3 , CN, or CF_3 ; and
 R^4 is hydrogen, halo, OCF_3 , CN, or CF_3 .

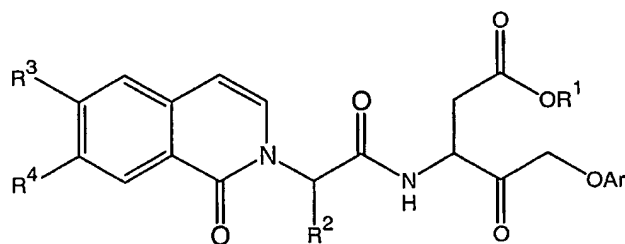
7. The compound according to claims 1 or 2,
 5 having the formula IB':



wherein:

R^2 is ethyl, n-propyl, or isopropyl;
 10 R^3 and R^4 are each independently hydrogen, halo,
 OCF_3 , CN, or CF_3 ; and
 Ar is trifluorophenyl or tetrafluorophenyl.

8. The compound according to claims 1 or 2,
 15 having the formula IB:



wherein:

R^1 is C_{1-6} straight chained or branched alkyl
 optionally substituted with phenyl or CF_3 ;
 20 R^2 is ethyl, n-propyl, or isopropyl;
 R^3 and R^4 are each independently hydrogen, halo,
 OCF_3 , CN, or CF_3 ; and
 Ar is trifluorophenyl or tetrafluorophenyl.

-90-

9. The compound according to claim 8, wherein Ar is 2,3,5,6-tetrafluorophenyl.

10. The compound according to any one of
5 claims 1-9, wherein R^2 is ethyl.

11. The compound according to any one of claims 1-10, wherein R^3 is H, and R^4 is F, Cl, or CF_3 .

10 12. The compound according to any one of claims 1-6 and 10-11 wherein when Y is halo, then R^3 and R^4 , are not simultaneously hydrogen.

13. The compound according to any one of
15 claims 1-12 wherein X is $-OR^1$ and the R^1 is an alkyl group that is not substituted with phenyl or CF_3 .

14. The compound according to any one of claims 1-13 wherein X is $-OR^1$ and the R^1 is ethyl or
20 propyl.

15. The compound according to any one of claims 1-5, 7, or 10-12 wherein X is $-N(R^5)_2$.

25 16. The compound according to claim 15 wherein X is $-N(R^5)_2$ and one R^5 is C_{1-6} straight chained or branched alkyl and the other R^5 is $-O-C_{1-6}$ straight chained or branched alkyl.

30 17. The compound according to claim 15 wherein X is $-N(R^5)_2$ and one R^5 is H or $-C_{1-6}$ straight chained or

-91-

branched alkyl and the other R⁵ is -C₁₋₆ straight chained or branched alkyl.

18. The compound according to any one of
5 claims 15-17 wherein R⁵ is methyl, ethyl, or propyl.

19. A compound selected from Table 1.

20. A pharmaceutical composition comprising:
10 a) a compound according to any one of claims 1-19; and
b) a pharmaceutically acceptable carrier, adjuvant or vehicle.

15 21. The composition according to claim 20, wherein said compound is selected from a compound according to any one of claims 1, 2, 5, 6, 7, 8, or 18.

22. A method for treating a disease in a
20 patient, wherein said disease is an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a disease associated
25 with cell death, an excess dietary alcohol intake disease, a viral mediated disease, retinal disorders, uveitis, inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis,
30 systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune

-92-

neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, atopic dermatitis, scarring, graft vs host disease, organ transplant rejection, organ apoptosis
5 after burn injury, osteoporosis, leukemias and related disorders, myelodysplastic syndrome, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, hemorrhagic shock,
10 sepsis, septic shock, burns, Shigellosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, Kennedy's disease, prion disease, cerebral ischemia, epilepsy, myocardial ischemia, acute and chronic heart disease, myocardial infarction, congestive heart failure,
15 atherosclerosis, coronary artery bypass graft, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related encephalitis, aging, alopecia, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, spinal cord injury, hepatitis-B,
20 hepatitis-C, hepatitis-G, yellow fever, dengue fever, Japanese encephalitis, various forms of liver disease, renal disease, polycystic kidney disease, H. pylori-associated gastric and duodenal ulcer disease, HIV infection, tuberculosis, or meningitis;

25 said method comprising the step of administering to said patient compound according to any one of claims 1-19 or a pharmaceutical composition according to any one of claims 20-21.

30 23. The method according to claim 22, wherein the disease is an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a

-93-

destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a disease associated with cell death, an excess dietary alcohol intake disease, a viral mediated disease, inflammatory peritonitis, glomerulonephritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, scarring, graft vs host disease, organ transplant rejection, organ apoptosis after burn injury, osteoporosis, leukemias and related disorders, myelodysplastic syndrome, metastatic melanoma, hemorrhagic shock, sepsis, septic shock, burns, Shigellosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, Kennedy's disease, prion disease, cerebral ischemia, epilepsy, myocardial ischemia, acute and chronic heart disease, myocardial infarction, congestive heart failure, atherosclerosis, coronary artery bypass graft, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related encephalitis, aging, alopecia, neurological damage due to stroke, traumatic brain injury, spinal chord injury, hepatitis-B, hepatitis-C, hepatitis-G, various forms of liver disease, renal disease, polycystic kidney disease, H. pylori-associated gastric and duodenal ulcer disease, HIV infection, tuberculosis, and meningitis.

25

24. The method according to claim 22, wherein the disease is neurological damage due to stroke, traumatic brain injury, spinal cord injury, Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, or cerebral ischemia.

30

-94-

25. The method according to claim 22, wherein the disease is osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, or neurological damage due to stroke.

26. The method according to claim 22, wherein the disease is an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a disease associated with cell death, an excess dietary alcohol intake disease, inflammatory peritonitis, osteoarthritis, pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, chronic active hepatitis, inflammatory bowel disease, Crohn's disease, psoriasis, atopic dermatitis, organ apoptosis after burn injury, hemorrhagic shock, sepsis, septic shock, burns, Alzheimer's disease, Parkinson's disease, Huntington's disease, cerebral ischemia, myocardial ischemia, acute and chronic heart disease, myocardial infarction, congestive heart failure, coronary artery bypass graft,

-95-

amyotrophic lateral sclerosis, multiple sclerosis,
alopecia, neurological damage due to stroke, ulcerative
colitis, traumatic brain injury, spinal cord injury,
hepatitis-B, hepatitis-C, hepatitis-G, various forms of
5 liver disease, or renal disease.

27. The method according to claim 22, wherein
said disease is a complication associated with a coronary
artery bypass graft.

10

28. A method for inhibiting a caspase-mediated
function in a patient comprising the step of
administering to said patient a compound according to any
one of claims 1-19 or a pharmaceutical composition
15 according to any one of claims 20-21.

29. The method according to claim 28, wherein
the function occurs in the central nervous system.

20

30. The method according to claim 28, for
decreasing IGIF or IFN- γ production in a patient.

31. The method according to claim 30, wherein
the IGIF or IFN- γ production is in the central nervous
25 system.

32. The method according to any one of claims
22-31 wherein said composition comprises an additional
therapeutic agent.

30

33. A method of preserving cells, said method
comprising the step of bathing the cells in a solution of

-96-

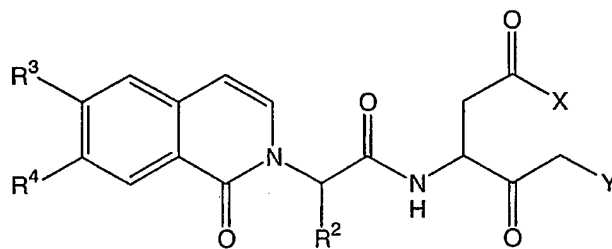
the compound according to any one of claims 1-19 or a pharmaceutically acceptable derivative thereof.

34. The method according to claim 33, wherein
5 said cells are in:

- a) an organ intended for transplant; or
- b) a blood product.

35. A method of treating cancer using
10 immunotherapy, wherein said immunotherapy comprises as a component thereof a compound according to any one of claims 1-19.

36. A process for preparing a compound of
15 formula I:



wherein:

- 20 X is -OR¹ or -N(R⁵)₂,
Y is halo, trifluorophenoxy, or tetrafluorophenoxy;
R¹ is:

C₁₋₆ straight chained or branched alkyl,
alkenyl, or alkynyl, wherein the alkyl, alkenyl, or
25 alkynyl is optionally substituted with optionally
substituted phenyl, CF₃, Cl, F, OMe, OEt, OCF₃, CN, or
NMe₂;

-97-

C₁₋₆ cycloalkyl, wherein 1-2 carbon atoms in the cycloalkyl is optionally replaced with -O- or -NR⁵-;

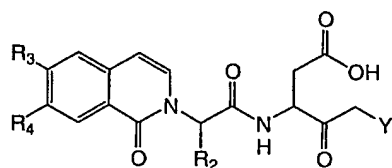
R² is C₁₋₆ straight chained or branched alkyl;

R³ is hydrogen, halo, OCF₃, CN, or CF₃;

5 R⁴ is hydrogen, halo, OCF₃, CN, or CF₃; and

R⁵ is H, C₁₋₆ straight chained or branched alkyl, aryl, -O-C₁₋₆ straight chained or branched alkyl, or -O-aryl;

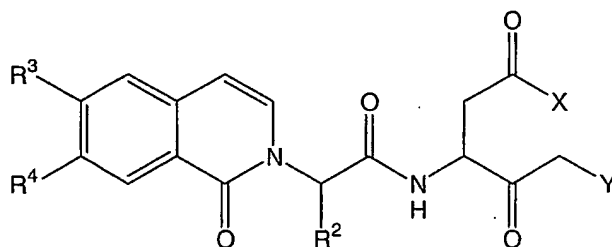
comprising the step of reacting a compound of
10 formula I':



I'

wherein X, Y, R², R³, and R⁴ are as defined for formula I;
under conditions forming an ester or amide bond to
15 provide a compound of formula I.

37. A process for preparing a compound of
formula I:



I

20

wherein:

X is -OR¹ or -N(R⁵)₂,

Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R¹ is:

-98-

C₁₋₆ straight chained or branched alkyl, alkenyl, or alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with optionally substituted phenyl, CF₃, Cl, F, OMe, OEt, OCF₃, CN, or NMe₂;

C₁₋₆ cycloalkyl, wherein 1-2 carbon atoms in the cycloalkyl is optionally replaced with -O- or -NR⁵-;

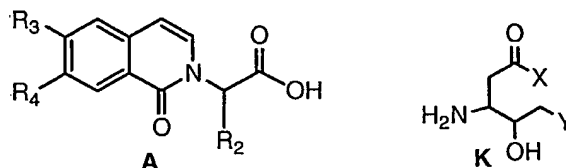
R² is C₁₋₆ straight chained or branched alkyl;

R³ is hydrogen, halo, OCF₃, CN, or CF₃;

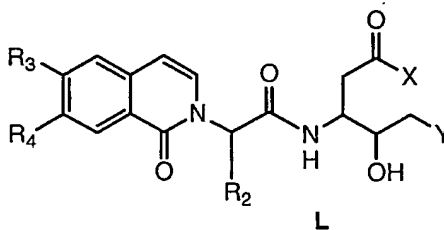
R⁴ is hydrogen, halo, OCF₃, CN, or CF₃; and

R⁵ is H, C₁₋₆ straight chained or branched alkyl, aryl, -O-C₁₋₆ straight chained or branched alkyl, or -O-aryl;

comprising the step of coupling a compound of formula A and a compound of formula K:



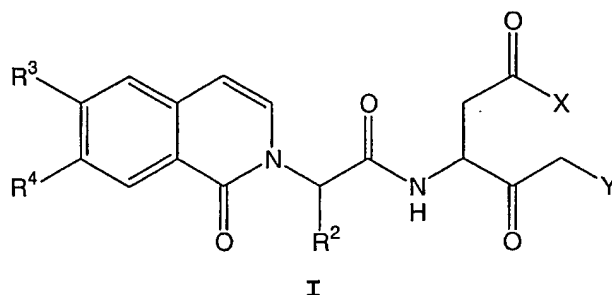
to provide a compound of formula L:



wherein X, Y, R¹, R², R³, and R⁴ are as defined in formula I and wherein the hydroxy group in K is optionally protected.

38. A process for preparing a compound of formula I:

-99-



wherein:

X is $-OR^1$ or $-N(R^5)_2$,

5 Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R^1 is:

C_{1-6} straight chained or branched alkyl, alkenyl, or alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with optionally substituted phenyl, CF_3 , Cl, F, OMe, OEt, OCF_3 , CN, or NMe_2 ;

10

C_{1-6} cycloalkyl, wherein 1-2 carbon atoms in the cycloalkyl is optionally replaced with $-O-$ or $-NR^5-$;

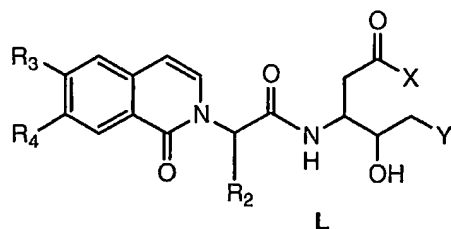
R^2 is C_{1-6} straight chained or branched alkyl;

15 R^3 is hydrogen, halo, OCF_3 , CN, or CF_3 ;

R^4 is hydrogen, halo, OCF_3 , CN, or CF_3 ; and

R^5 is H, C_{1-6} straight chained or branched alkyl, aryl, $-O-C_{1-6}$ straight chained or branched alkyl, or $-O-$ aryl;

20 comprising the step of oxidizing a compound of formula L:



wherein X, Y, R^1 , R^2 , R^3 , and R^4 are as defined for formula I; to provide a compound of formula I.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/40870

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D217/24 A61K31/472 A61K31/4725 C07D401/12 C07D405/12
C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/42216 A (BINCH HAYLEY ;GOLEC JULIAN (GB); CHARRIER JEAN DAMIEN (GB); VERTEX) 14 June 2001 (2001-06-14) cited in the application page 73 -page 74; claim 1 page 76 -page 77; claims 9,10 page 7, line 14 - line 20 page 33 -page 34; example 9: the tert-butyl ester of the compound of example 9 (cf., steps (D) and (E) of example 1) ---	1-38
A	WO 01/94351 A (BRENCHLEY GUY ;CHARRIER JEAN DAMIEN (GB); VERTEX PHARMA (US)) 13 December 2001 (2001-12-13) the whole document; in particular, page 11, line 16 - page 12, line 10; and page 23, line 12 - line 30 ---	1-38
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A' document defining the general state of the art which is not considered to be of particular relevance
- *E' earlier document but published on or after the international filing date
- *L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O' document referring to an oral disclosure, use, exhibition or other means
- *P' document published prior to the international filing date but later than the priority date claimed

- *T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8' document member of the same patent family

Date of the actual completion of the international search

12 May 2004

Date of mailing of the international search report

19/05/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/40870

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/002961 A (MORTIMORE MICHAEL ;KNEGTEL RONALD (GB); MILLAN DAVID (GB); STUDLEY) 8 January 2004 (2004-01-08) page 22; the compound of formula III, and lines 8-10 -----	1-38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/40870

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 22-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/40870

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0142216	A	14-06-2001	AU 2428301 A	18-06-2001
			BR 0016282 A	27-08-2002
			CA 2393710 A1	14-06-2001
			CN 1420872 T	28-05-2003
			CZ 20021970 A3	16-10-2002
			EP 1244626 A2	02-10-2002
			HU 0300782 A2	29-09-2003
			JP 2003516393 T	13-05-2003
			NO 20022656 A	06-08-2002
			NZ 519424 A	26-03-2004
			SK 8072002 A3	04-02-2003
			WO 0142216 A2	14-06-2001
			ZA 200204390 A	02-06-2003
WO 0194351	A	13-12-2001	AU 7527901 A	17-12-2001
			CA 2409015 A1	13-12-2001
			EP 1289993 A1	12-03-2003
			JP 2003535865 T	02-12-2003
			WO 0194351 A1	13-12-2001
			US 2002045623 A1	18-04-2002
WO 2004002961	A	08-01-2004	WO 2004002961 A1	08-01-2004
			US 2004072850 A1	15-04-2004